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Synthesis

A new one-pot three-component synthesis of 4-aryl-6-cycloamino-1,3,5-triazin-2-amines under microwave irradiation

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A New One-Pot Three-component Synthesis of 4-Aryl-6-cycloamino-1,3,5-triazin-2-amines under Microwave Irradiation

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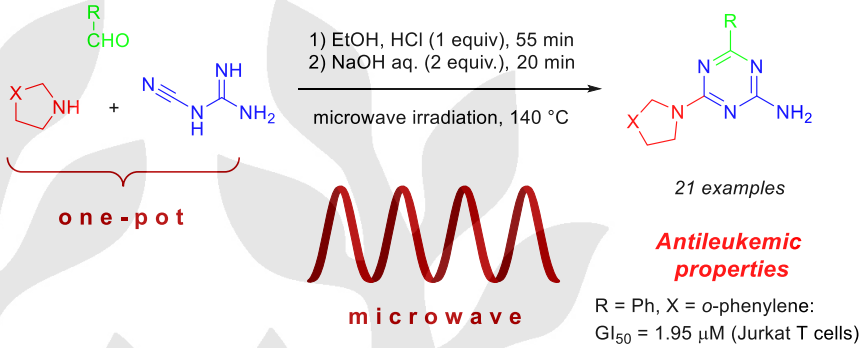
Dedicated to the memory of Professor Boris Syropyatov (6 Nov 1940 – 24 Oct 2020)



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Abstract A new method for the fast synthesis of diverse 4-aryl-6-cycloamino-1,3,5-triazin-2-amines was developed. The synthesis is performed under microwave irradiation in a one-pot manner from cyanoguanidine, aromatic aldehydes, and cyclic amines. Their three-component reaction in the presence of hydrochloric acid produced dihydrotriazines, which were then converted (without isolation) to the targeted compounds *via* aromatic dehydrogenation in the presence of alkali. The reaction tolerated various aromatic aldehydes (including heterocyclic) and cyclic amines. Crystal structures of two representative 4-aryl-6-morpholino-1,3,5-triazin-2-amines were established by X-ray crystallography. The results of preliminary biological screening identified potent antileukemic activity for 6-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4-phenyl-1,3,5-triazin-2-amine.

Key words Triazines, Multicomponent reactions, Microwave-assisted synthesis, Dehydrogenative aromatization; Antiproliferative activity

1,3,5-Triazines have been one of the most widely used classes of herbicides for the last half-century.[1] In veterinary medicine, triazines (including 1,3,5-triazines toltrazuril and ponazuril) form a well-established class of antiprotozoal drugs.[2] In the contemporary design of new bioactive compounds with potential therapeutic applications, the 1,3,5-triazine ring has also proven to be a privileged scaffold.[3-5] Despite a wide range of biological activities reported for 1,3,5-triazines, achievements in the development of anticancer agents based on this skeleton were particularly important.[6,7] Recently approved anticancer drugs include 1,3,5-triazines Enasidenib[8,9] and Gedatolisib[10,11] (Fig. 1). The 1,3,5-triazine ring of these drugs is decorated in positions 2, 4, and 6 with two substituted amino groups and a (het)aryl moiety. The inhibitors of Bruton's tyrosine kinase[12] and lysophosphatidic acid acyltransferase β[13-15] and recently reported[16] highly potent and selective agents targeting triple-negative breast cancer share a similar 4-(het)aryl-6-arylamino-1,3,5-triazin-2-amine scaffold. Structurally related compounds with 6-aralkylamino substitution demonstrated potent inhibition of tryptophan hydroxylase[17] and an effective positive allosteric modulation of G protein-coupled receptor 68 (GPR68).[18,19] The inhibitors of phosphoinositide 3-kinase[20] and ligands for H_4 histamine receptors[21,22] were found among 4-aryl-6-cycloamino-1,3,5-triazin-2-amines, while similar 4-aralkyl-6-cycloamino-1,3,5-triazin-2-amines selectively bound to 5-HT_6 serotonin receptors.[23]

The pharmacological investigation of 4-aryl-6-cycloamino-1,3,5-triazin-2-amines (**1**) possessing different substitution patterns would open opportunities for the identification of new potent bioactive agents. However, existing methods for the preparation of these compounds are limited and do not allow fast synthesis of sufficiently diverse molecules.

One of the methods for the synthesis of 4-aryl-6-cycloamino-1,3,5-triazin-2-amines (**1**) utilizes cyanuric chloride, which is involved in a sequential nucleophilic substitution with cyclic amines (*e.g.* morpholine) and then ammonia; the Suzuki cross-coupling of the resulting intermediate with arylboronic acids concludes this approach (Scheme 1, Route 1).[20]

Another general approach for the synthesis of **1** relies on the reactions of biguanides, derived from cyanoguanidine and cyclic amines, with different reagents (Route 2). The reaction of biguanides with benzoin is highly sensitive to pH and structure substrates[24] making the scope of this method for the preparation of 4-aryl-6-cycloamino-1,3,5-triazin-2-amines

limited. The condensation of biguanides with carboxylic acid derivatives, *e.g.* esters in the presence of strong bases, is the most common method for the synthesis of **1**.[25] Recently, *N*,*N*-dimethyl-substituted amides were employed in the imidazolium-catalyzed reaction with biguanides resulting in the triazine ring closure.[26] However, this reaction was more applicable to DMF as a one-carbon inserting synthon and only one 4-aryl derivative was prepared by this method.[26] Benzyl alcohols were reported to react with biguanides under the ruthenium[27] or graphene oxide[28] catalysis affording 4-aryl-6-cycloamino-1,3,5-triazin-2-amines (**1**). Being more general in scope, these methods suffer from relatively long reaction time (heating for up to 30 h in the second step).

Recently, we developed a new method for the synthesis of 6,N^2-diaryl-1,3,5-triazin-2,4-diamines (**3**) *via* one-pot three-component condensation, followed by the Dimroth rearrangement and dehydrogenative aromatization of the dihydrotriazine intermediate **2** (Scheme 2).[29] This method was efficiently applied to a wide range of substrates and afforded compounds with significant anticancer activity.[30] The three-component synthesis of dihydrotriazines **4** has not been reported. Moreover, secondary amines and all aliphatic amines failed to afford dihydrotriazines in earlier attempts[31] to involve them in the three-component reaction with cyanoguanidine and aldehydes. Nevertheless, we decided to attempt performing the three-component synthesis of **4** under microwave irradiation also suggesting that upon heating in the presence of a base, these intermediate would undergo dehydrogenative aromatization to afford the desired triazines **1** (Scheme 2). Performing both of these transformations in a one-pot manner would make this method more practical for the fast synthesis of diverse 4-aryl-6-cycloamino-1,3,5-triazin-2-amines (**1**). Microwave irradiation has demonstrated a great utility in the multicomponent reactions[32] and for the preparation of 1,3,5-triazines[33] improving the efficiency of synthetic procedures. Herein we report the development of a new method for the synthesis of 4-aryl-6-cycloamino-1,3,5-triazin-2-amines (**1**) *via* the proposed approach under microwave irradiation.

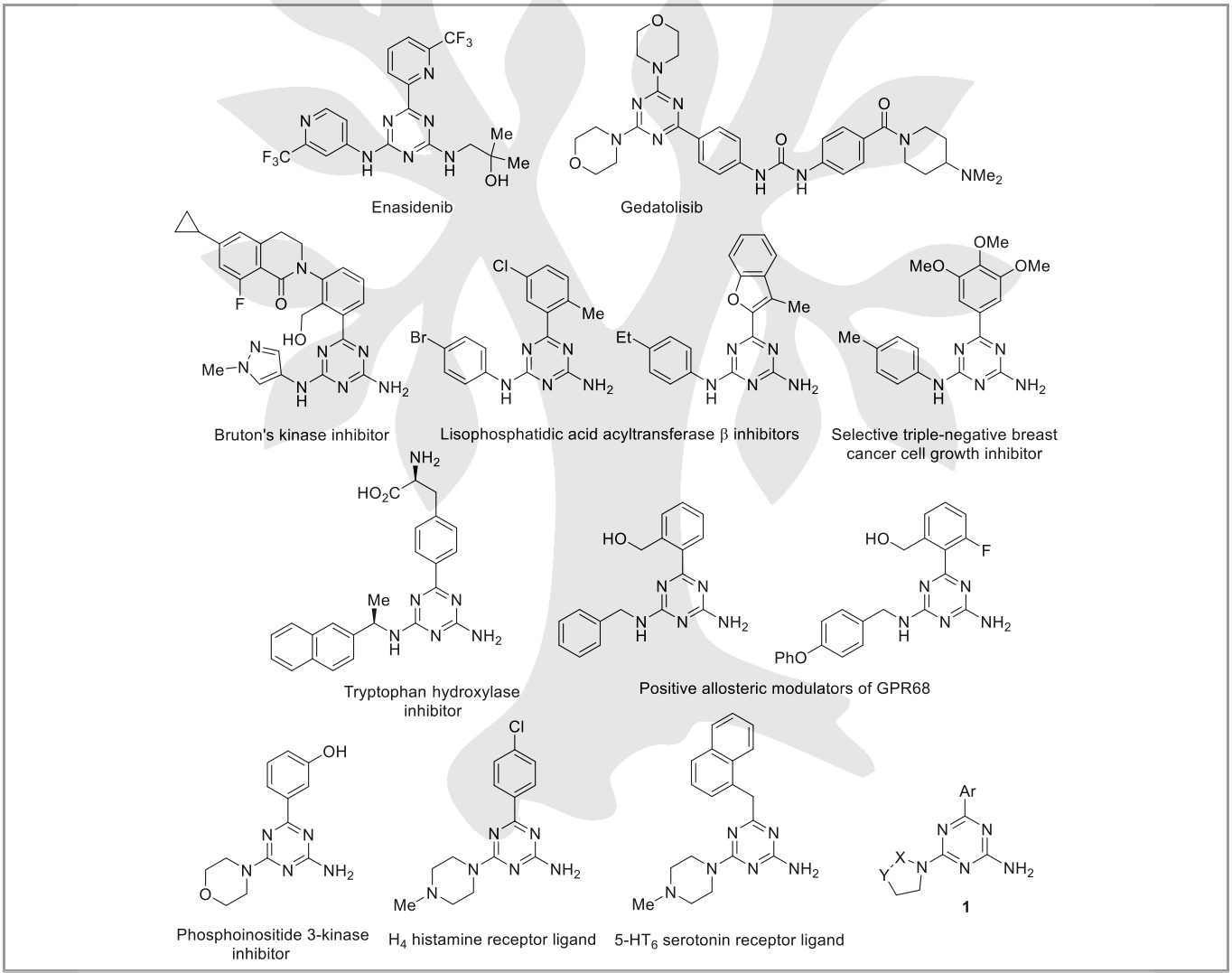
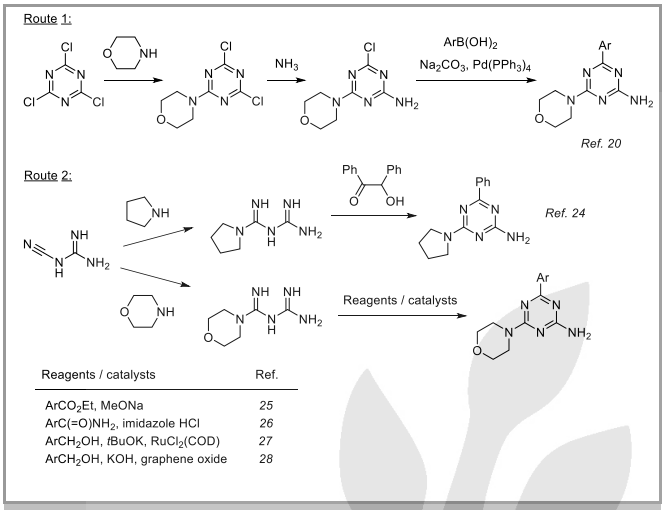
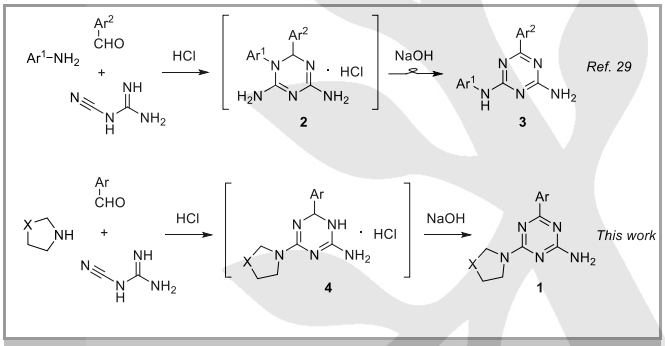


Figure 1 Selected bioactive 1,3,5-triazines.



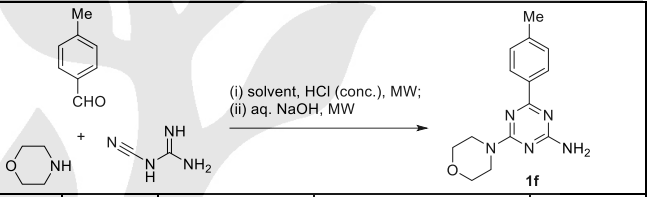
Scheme 1 Reported methods for the synthesis of 4-aryl-6-cycloamino-1,3,5-triazin-2-amines.



Scheme 2 One-pot three-component synthesis of 6,N^2-diaryl-1,3,5-triazin-2,4-diamines (**3**) and proposed synthesis of 4-aryl-6-cycloamino-1,3,5-triazin-2-amines (**1**).

For the trial reaction and the subsequent condition optimization, we utilized the model reaction of cyanoguanidine with *p*-tolualdehyde and morpholine under controlled microwave irradiation in a Monowave 400 reactor (Anton Paar, Austria) (Table 1). Replicating the reaction conditions from our protocol developed earlier for the synthesis of 6,N^2-diaryl-1,3,5-triazin-2,4-diamines (**3**),[29] we were delighted to observe the formation of desired product **1f**, which was easily isolated by simple filtration in 37% yield (Table 1, entry 2). Changing the solvent from EtOH to MeOH or PrOH resulted in lower yields (entries 1 and 3). Attempts to increase or decrease the reaction temperature also had a negative impact on yields of **1f** (entries 4 and 5) and further optimization was continued at 140 °C using EtOH as a reaction medium. It was found that an increase in the duration of the first step benefited the reaction outcome improving the yield to 44% in 55 min (entry 6). Further improvement to 48% yield was achieved extending the duration of the second step to 20 min (entry 7). The longer duration of the second step resulted in lower yields, probably due to the gradual degradation of the product under the reaction conditions (entry 8 and 9). The addition of another equivalent of *p*-tolualdehyde at any of the steps did not improve the reaction outcome (entries 10 and 11). At the same time, the base appeared to play a critical role in the second step. The detrimental effect to the reaction outcome was observed when sodium hydroxide was applied in the second step in the quantity equimolar to hydrochloric acid added in the first step (entry 12). Heating without microwave irradiation under otherwise similar conditions using a Monowave 50 reactor resulted in some decrease in the yield of **1f** (entry 13). Therefore, microwave conditions allowing isolation of **1f** in 48% yield (entry 7) were used for the exploration of the reaction scope (more detailed optimization results are available in Supporting Information Table S1). It should be also noted that unlike in the synthesis of N^2-aryl analogs of **4**,[34] we were unable to isolate intermediate **4** after the first step.

Table 1 Optimization of reaction conditions for the synthesis of 4-(4-methylphenyl)-6-morpholino-1,3,5-triazin-2-amine (**1f**) under microwave irradiation.[a]

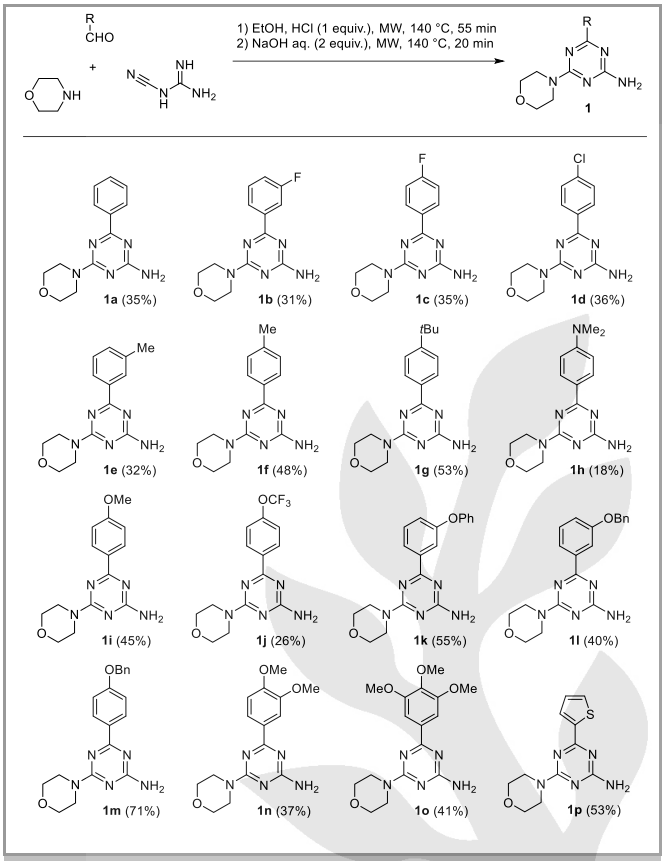


Entry	Solvent	Temp, °C	Reaction time, min		Yield,[b] %
			(i)	(ii)	
1	MeOH	140	20	15	33
2	EtOH	140	20	15	37
3	PrOH	140	20	15	9
4	EtOH	130	20	15	28
5	EtOH	150	20	15	31
6	EtOH	140	55	15	44
7	EtOH	140	55	20	48
8	EtOH	140	55	25	46
9	EtOH	140	55	60	41
10[c]	EtOH	140	55	20	33
11[d]	EtOH	140	55	20	26
12[e]	EtOH	140	55	20	6
13[f]	EtOH	140	55	20	33

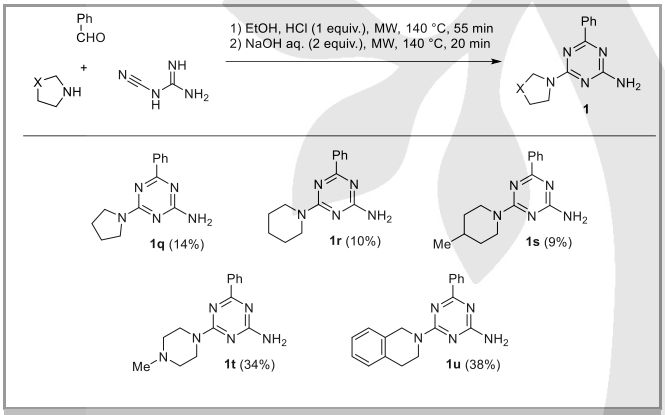
[a] The reactions were performed in a Monowave 400 microwave reactor (Anton Paar, Austria) using cyanoguanidine (2.5 mmol), *p*-tolualdehyde (2.5 mmol), morpholine (2.5 mmol), and conc. HCl (2.5 mmol) in 2 mL of the specified solvent in step (i) and addition of 1 mL of 5 N NaOH (aq.) in step (ii).
[b] Isolated yield calculated on the basis of cyanoguanidine.
[c] The reaction was carried out using 5 mmol of *p*-tolualdehyde.
[d] Another 2.5 mmol of *p*-tolualdehyde was added to the reaction mixture in step (ii).
[e] 0.5 mL of 5 N NaOH (aq.) [2.5 mmol] was used in step (ii).
[f] The reaction was performed in a Monowave 50 reactor (Anton Paar, Austria) without microwave irradiation.

In the exploration of the method scope, different aromatic aldehydes and cyclic amines were examined. The reaction of cyanoguanidine and morpholine with benzaldehydes tolerated various substituents in the aldehyde aromatic ring (Scheme 3). Moreover, heteroaromatic thenaldehyde was also successfully involved in the reaction affording **1p** in 53% yield.

Examining the scope of cyclic amines for the reaction, we found that in the three-component reaction with cyanoguanidine and benzaldehyde, morpholine could be replaced by pyrrolidine, piperidines, *N*-methylpiperazine, or tetrahydroisoquinoline thus affording corresponding 6-cycloamino-4-phenyl-1,3,5-triazin-2-amines (**1q-u**) (Scheme 4).

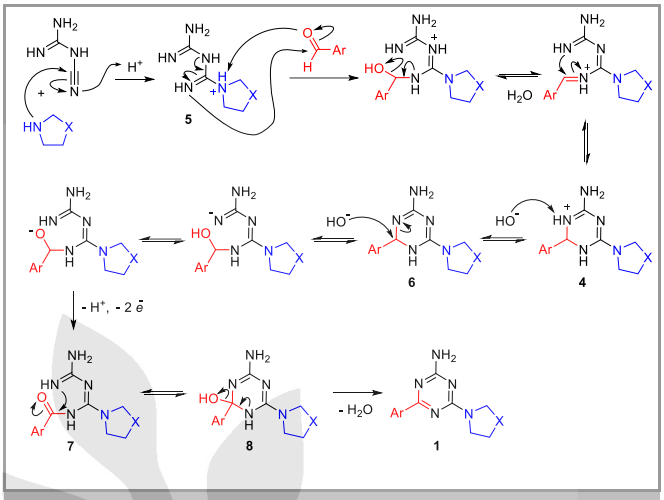


Scheme 3 Scope of aromatic aldehydes for the synthesis of 4-aryl-6-morpholino-1,3,5-triazin-2-amines (**1a-p**).



Scheme 4 Scope of cyclic amines for the synthesis of 4-phenyl-6-cycloamino-1,3,5-triazin-2-amines (**1q-u**).

The proposed mechanism for the synthesis of **1** is outlined in Scheme 5. In the first step, the addition of a cyclic amine to the acid-activated nitrile group of cyanoguanidine is followed by the reaction of the formed biguanide **5** with an aldehyde resulting in the dihydrotriazine ring closure and formation of the intermediate **4**. In the presence of alkali, it converts to the *N*-Mannich base **6**, which undergoes dehydrogenative aromatization resulting in the formation of **1**. It is proposed that the aromatization involves initial ring-opening by the alkali, oxidation to the *N*-acylbiganide **7**, recyclization to **8,** and subsequent dehydration affording the desired product **1**.



Scheme 5 Proposed mechanism for the synthesis of 4-aryl-6-cycloamino-1,3,5-triazin-2-amines (**1**).

The NMR spectroscopic data for the prepared compounds support proposed structure **1**. In the ^{13}C NMR spectra of **1**, the three downfield signals at 164.4-169.7 ppm confirm the formation of an electron-deficient aromatic 1,3,5-triazine ring.

Due to extended conjugation, the triazine and a phenyl ring directly attached to it are coplanar. This results in a significant downfield shift of the ^{1}H NMR spectra signals attributed to phenyl protons located in *ortho*-positions to the triazine and experiencing its anisotropic effect.

The electron-deficient nature of the triazine ring results in significant delocalization of electrons from the adjacent amino groups. The protons of the primary amino group in position 2 are therefore deshielded and their signal in ^{1}H NMR spectra appear at 6.71-7.01 ppm. The electron delocalization of the cycloamino nitrogen atom is particularly visible in the NMR spectra of **1q**, which possesses a relatively more rigid pyrrolidine ring. This delocalization implies a partial double bond character of the C-N bond connecting the rings. In ^{1}H and ^{13}C NMR spectra of **1q**, the restricted rotation around this bond manifests in individual signals for magnetically non-equivalent atoms of the opposite sides of the symmetrical pyrrolidine ring.

The ^{1}H NMR spectrum of **1s** also confirms the substantial delocalization of the lone pair of the piperidine nitrogen over the triazine ring. The methyl group in position 4 of the piperidine ring stabilizes its chair conformation with substituents occupying equatorial positions. The chemical shifts and coupling for the signals of the remaining protons also confirm the chair conformation of the piperidine[35] in **1s**. Additionally, the equatorial protons at carbon atoms adjacent to the piperidine nitrogen occur in the plane of the triazine ring and due to restricted rotation become magnetically non-equivalent. Therefore, in the ^{1}H NMR spectrum of **1s**, these protons give two independent signals downfield-shifted to 4.72-4.81 ppm ($\Delta\delta\approx1.7$-1.8 ppm from the signals of the same protons in 4-methylpiperidine[36]) due to the anisotropic effect of the triazine ring. The axial protons at the same carbon atoms are affected significantly less ($\Delta\delta\approx0.3$ ppm). At higher temperatures (35 °C), two broad signals of the equatorial α-CH coalesce into a single peak still suggesting slow rotation around the C-N bond between the triazine and piperidine rings due to the lone pair

delocalization (Fig. 2). Upon further heating, the signal the equatorial α-CH transforms into the expected doublet with $^2J_{gem}$=-13 Hz. Due to the 1,4-substitution of the piperidine ring in **1s**, its chair conformation remains stable at these temperatures.

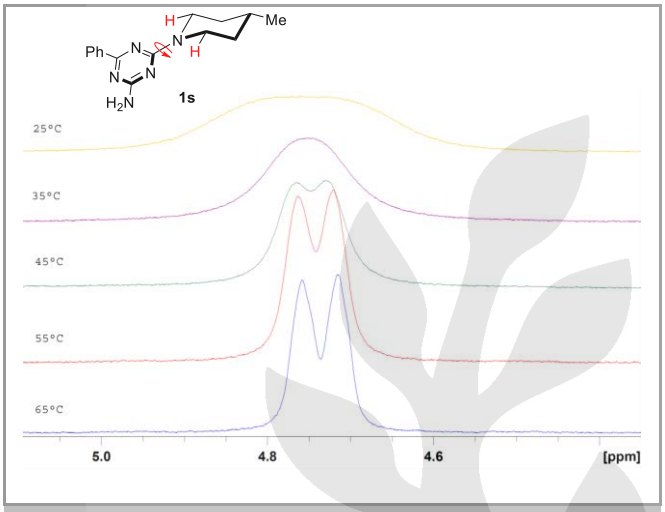


Figure 2 Restricted rotation around the C-N bond between the triazine and piperidine rings in **1s**: signals of the equatorial α-CH of piperidine in dynamic ^{1}H NMR spectra.

The structural assignments were further confirmed by X-ray crystallography data for two representative compounds **1l** and **1n**; their molecular structures are illustrated in Fig. 3. In **1l**, the six atoms comprising the triazine ring are planar, exhibiting a r.m.s. deviation = 0.0074 Å. The pendent phenyl ring is inclined to the central plane [N3C3/C6 dihedral angle = 26.77(5)°] and the dihedral angle between the triazine ring and the best plane through the morpholine ring (chair conformation) of 5.89(7)° is indicative of approximately co-planar relationship. The (benzyloxy)phenyl residue is twisted as seen in the dihedral angle between the rings of 79.47(4)°. The terminal ring lies in a position orientated towards the bay region of the molecule defined by the triazine and two connected rings, and is orthogonal to the central plane forming a dihedral angle of 88.80(3)°. Within the ring, the C–N bond lengths span a relatively narrow range, *i.e.* 1.3293(14) Å for C4–N5 to 1.3546(14) Å for C2–N3, consistent with considerable delocalization of π-electron density over the ring; the exocyclic C2–N2 bond [1.3429(14) Å] lies within this range.

The molecular structure of **1n**, Fig. 3(b), presents similar features to that of **1l**. The r.m.s. deviation for the six atoms comprising triazine ring = 0.0090 Å. The dihedral angles between the central plane and the attached phenyl [11.28(5)°] and morpholine [5.10(5)°; chair conformation] rings indicate, to a first approximation, co-planar relationships. The molecule has the shape of the letter, U. Within the triazine ring, significant delocalization of π-electron density is indicated as the range of C–N bond lengths is less than for **1l**, *i.e.* 1.3318(16) Å for C4–N3 to 1.3529(16) Å for C2–N3, and, again, as for **1l**, there is no pattern of alternating short and long C–N bonds within the triazine ring; the C2–N2 bond length is 1.3366(16) Å.

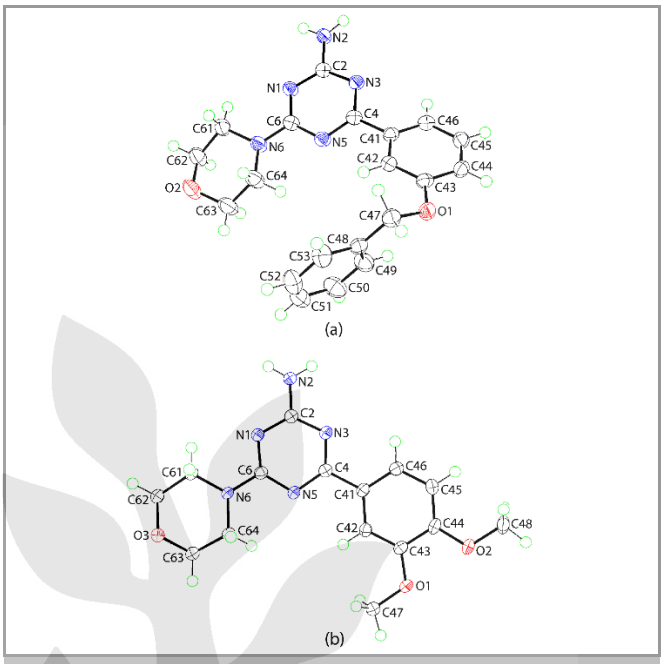


Figure 3 Molecular structures of (a) **1l** and (b) **1n** showing atom labeling scheme and 70% anisotropic displacement parameters.

In the molecular packing of **1l**, amine-N–H···N(triazine) hydrogen bonding assembles centrosymmetrically-related molecules into dimeric aggregates through eight-membered {···HNCN}$_2$ supramolecular synthons, Fig. 4(a); geometric parameters characterizing the key interatomic contacts are given in the caption of Supporting Information Fig. S1. The aggregates thus formed are linked into a supramolecular tape, approximately along [1 3 0], by amine-N–H···O(ether) hydrogen bonds. The connections between tapes to form a layer in the ab-plane are π-stacking interactions between triazine and C41-phenyl rings as detailed in Supporting Information Fig. S1; layers stack along the c-axis without directional interactions between them.

A more complicated expansion of supramolecular association is evident in the crystal of **1n** whereby each molecule is connected to four symmetry-related molecules by conventional hydrogen bonding. Thus, the hydrogen bonds prominent in the molecular packing are amine-N–H···O(morpholine) and amine-N–H···N(triazine), and lead to the formation of a two-dimensional array in the ac-plane, Fig. 4(b); see the caption of Supporting Information Fig. S2 for geometric details. Additional stabilization to the layer is afforded by morpholine-C–H···O(methoxy) and morpholine-C–H···π(phenyl) contacts. The layers stack along the b-axis with the directional interactions to consolidate the three-dimensional packing being methyl-C–H···O(methoxy) and π-stacking interactions between triazine and C41-phenyl rings; a view of the unit-cell contents is shown in Supporting Information Fig. S2.

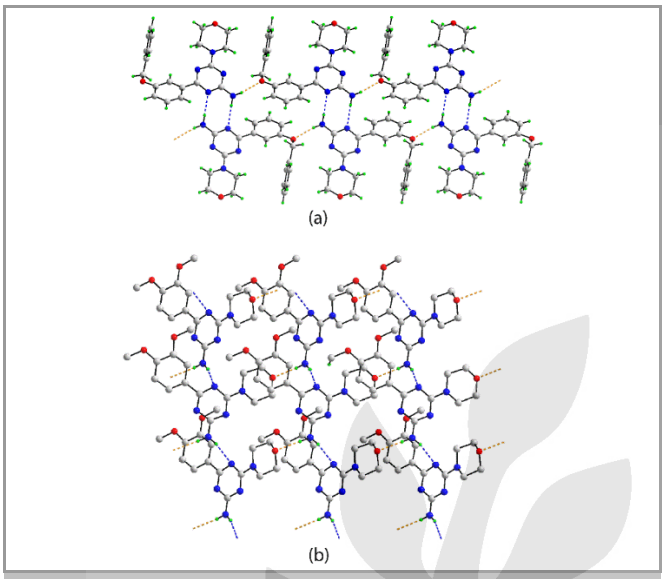


Figure 4 Supramolecular association sustained by conventional hydrogen bonds in **1l** and **1n**: (a) the supramolecular tape in the crystal of **1l** and (b) supramolecular layer in the crystal of **1n** (non-participating hydrogen atoms have been omitted for clarity). The N–H···O and N–H···N hydrogen bonds are represented by orange and blue dashed lines, respectively.

The prepared compounds were screened for antiproliferative activity against a Jurkat-T cell line at 10 μM. The most potent compound identified in the screening was 6-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4-phenyl-1,3,5-triazin-2-amine (**1u**), which was further tested at several concentrations (Supporting Information, Fig. S3) to estimate the 50% growth inhibition (GI_{50}) value. Typical antileukemic drugs mercaptopurine, methotrexate, and cytarabine were used as positive controls. It was found that **1u** inhibited cell proliferation in a concentration-dependent manner demonstrating the GI_{50} value of 1.95±0.25 μM. Being more potent than mercaptopurine (GI_{50} = 11.12 ± 4.89 μM), **1u** was less effective than methotrexate (GI_{50} = 0.37 ± 0.03 μM) and cytarabine (GI_{50} = 0.29 ± 0.01 μM). Nevertheless, these results indicate that the search for new antileukemic agents among 4-aryl-6-cycloamino-1,3,5-triazin-2-amines could be fruitful.

In conclusion, we developed a new method for the fast one-pot synthesis of diverse 4-aryl-6-cycloamino-1,3,5-triazin-2-amines. This method is based on two processes: (1) acid-catalyzed three-component condensation of cyanoguanidine, aromatic aldehydes, and cyclic amines and (2) dehydrogenative aromatization in the presence of a base. Overall, the method was found to be rather general, with similar efficacy applicable to various aldehydes and cyclic amines. The main advantage of the method is the potential for quick and convenient access to structurally diverse 4-aryl-6-cycloamino-1,3,5-triazin-2-amines for their biological evaluations. Preliminary data from the antileukemic screening of prepared 4-aryl-6-cycloamino-1,3,5-triazin-2-amines were promising. Further investigations are under way and the results will be reported in due course.

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General information

Melting points (uncorrected) were determined on a Stuart™ SMP40 automatic melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Fourier NMR spectrometer (300 MHz) using DMSO-d_6 as a solvent and TMS as an internal reference. Microwave-assisted reactions were carried out in the closed vessel focused single mode using a Monowave 400 microwave synthesizer (Anton Paar, Austria) monitoring reaction temperature by the equipped IR sensor. The control experiment using conventional heating was performed in a Monowave 50 (Anton Paar, Austria) reactor.

General procedure for the preparation of 4-aryl-6-cycloamino-1,3,5-triazin-2-amines (1).

To a solution of cyanoguanidine (0.21 g, 2.5 mmol), (het)arylaldehyde (2.5 mmol) and cyclic amine (2.5 mmol) in EtOH (2 mL) in a 10 mL seamless pressure vial, conc. HCl (0.21 mL, 2.5 mmol) was added. The reaction mixture was irradiated in the Monowave 400 (Anton Paar, Austria) microwave reactor operating at maximal microwave power up to 850 W at 140 °C for 55 min. After cooling to rt, an aq. solution of NaOH (5 N, 1 mL) was added to the reaction mixture and irradiation continued for another 20 min at 140 °C. After cooling, the precipitated product was filtered, washed with water and recrystallized from an appropriate solvent affording desired products **1**.

*6-Morpholino-4-phenyl-1,3,5-triazin-2-amine (**1a**).*

White solid; yield 224 mg (35%); mp 119-121 °C (EtOH), lit.[37] 121-123 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.63-3.67 (4H, *m*, CH_2OCH_2), 3.80 (4H, *br s*, CH_2NCH_2), 6.94 (2H, *br s*, NH_2), 7.43-7.55 (3H, *m*, H-3′, H-4′, and H-5′), 8.28-8.32 (2H, *m*, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2NCH_2), 65.9 (CH_2OCH_2), 127.7 (2C), 128.1 (2C), 131.2, 136.8, 164.9 (C-6), 167.1 (C-2), 169.6 (C-4). Anal. Calcd for $C_{13}H_{15}N_5O$: C, 60.69; H, 5.88; N, 27.22. Found: C, 60.54; H, 5.93; N, 27.07.

*4-(3-Fluorophenyl)-6-morpholino-1,3,5-triazin-2-amine (**1b**).*

White solid; yield 215 mg (31%); mp 143-144 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.63-3.68 (4H, *m*, CH_2OCH_2), 3.80 (4H, *br s*, CH_2NCH_2), 7.03 (2H, *br s*, NH_2), 7.37 (1H, *ddt*, *J* = 0.9, 2.7, 8.5 Hz, H-4′), 7.53 (1H, *ddd*, *J* = 6.0, 8.0, 8.0 Hz, H-5′), 8.01 (1H, *ddd*, *J* = 1.4, 2.7, 10.6 Hz, H-2′), 8.14 (1H, *ddd*, *J* = 1.2, 1.2, 7.8 Hz, H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2NCH_2), 65.9 (CH_2OCH_2), 114.0 (*d*, *J* = 22.9 Hz), 118.0 (*d*, *J* = 21.1 Hz), 123.7 (*d*, *J* = 3.0 Hz), 130.2 (*d*, *J* = 7.5 Hz), 139.6 (*d*, *J* = 7.5 Hz), 162.1 (*d*, *J* = 242.2 Hz), 164.8 (C-6), 167.1 (C-2), 168.5 (*d*, *J* = 3.1 Hz, C-4). Anal. Calcd for $C_{13}H_{14}FN_5O$: C, 56.72; H, 5.13; N, 25.44. Found C, 56.55; H, 5.20; N, 25.32.

*4-(4-Fluorophenyl)-6-morpholino-1,3,5-triazin-2-amine (**1c**).*

White solid; yield 239 mg (35%); mp 186-187 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.63-3.67 (4H, *m*, CH_2OCH_2), 3.79 (4H, *br s*, CH_2NCH_2), 6.96 (2H, *br s*, NH_2), 7.29 (2H, *dd*, *J* = 8.8, 8.8 Hz, H-3′ and H-5′), 8.35 (2H, *dd*, *J* = 5.9, 8.7 Hz, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2NCH_2), 65.9 (CH_2OCH_2), 115.0 (2C, *d*, *J* = 21.6 Hz), 130.1 (2C, *d*, *J* = 8.9 Hz), 133.3 (*d*, *J* = 2.2 Hz), 164.1 (*d*, *J* = 248.3), 164.8 (C-6), 167.1 (C-2), 168.7 (C-4). Anal. Calcd for $C_{13}H_{14}FN_5O$: C, 56.72; H, 5.13; N, 25.44. Found: C, 56.59 H, 5.20; N, 25.32.

*4-(4-Chlorophenyl)-6-morpholino-1,3,5-triazin-2-amine (**1d**).*

Yellowish solid; yield 264 mg (36%); mp 203-204 °C (EtOH), lit.[38] 198-201 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.63-3.67 (4H, *m*, CH_2OCH_2), 3.79 (4H, *br s*, CH_2NCH_2), 6.99 (2H, *br s*, NH_2), 7.54 (2H, *d*, *J* = 8.7 Hz, H-3′ and H-5′), 8.30 (2H, *d*, *J* = 8.7 Hz, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2NCH_2), 65.9 (CH_2OCH_2), 128.2 (2C), 129.5 (2C), 135.7, 136.0, 164.8 (C-6), 167.1 (C-2), 168.7 (C-4). Anal. Calcd for $C_{13}H_{14}ClN_5O$: C, 53.52; H, 4.84; N, 24.01. Found: C, 53.39; H, 4.97; N, 23.94.

*4-(3-Methylphenyl)-6-morpholino-1,3,5-triazin-2-amine (**1e**).*

White solid; yield 216 mg (32%); mp 151-152 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.39 (3H, *s*, Me), 3.64-3.69 (4H, *m*, CH_2OCH_2), 3.82 (4H, *br s*, CH_2NCH_2), 6.97 (2H, *br s*, NH_2), 7.32-7.40 (2H, *m*, H-4′ and H-5′), 8.10-8.17 (2H, *m*, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0 (Me), 43.1 (CH_2NCH_2), 66.0 (CH_2OCH_2), 125.0, 128.0, 128.2, 131.8, 136.8, 137.2, 164.9 (C-6), 167.1 (C-2), 169.7 (C-4). Anal. Calcd for $C_{14}H_{17}N_5O$: C, 61.98; H, 6.32; N, 25.81. Found: C, 61.85; H, 6.45; N, 25.69.

*4-(4-Methylphenyl)-6-morpholino-1,3,5-triazin-2-amine (**1f**).*

White solid; yield 324 mg (48%); mp 167-168 °C (EtOH), lit.[25] 167 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.37 (3H, *s*, Me), 3.63-3.67 (4H, *m*, CH_2OCH_2), 3.79 (4H, *br s*, CH_2NCH_2), 6.92 (2H, *br s*, NH_2), 7.27 (2H, *d*, *J* = 8.0 Hz, H-3′ and H-5′), 8.20 (2H, *d*, *J* = 8.2 Hz, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.0 (Me), 43.1 (CH_2NCH_2), 65.9 (CH_2OCH_2), 127.8 (2C), 128.7 (2C), 134.1, 141.0, 164.9 (C-6), 167.1 (C-2), 169.6 (C-4). Anal. Calcd for $C_{14}H_{17}N_5O$: C, 61.98; H, 6.32; N, 25.81. Found: C, 61.88; H, 6.41; N, 25.73.

*4-(4-(tert-Butyl)phenyl)-6-morpholino-1,3,5-triazin-2-amine (**1g**).*

White solid; yield 418 mg (53%); mp 178-179 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.31 (9H, *s*, C(*Me*)$_3$), 3.63-3.67 (4H, *m*, CH_2OCH_2), 3.78 (4H, *br s*, CH_2NCH_2), 6.91 (2H, *br s*, NH_2), 7.48 (2H, *d*, *J* = 8.6 Hz, H-3′ and H-5′), 8.21 (2H, *d*, *J* = 8.6 Hz, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.9 (C(*Me*)$_3$), 34.5 (*C*(Me)$_3$), 43.0 (CH_2NCH_2), 65.9 (CH_2OCH_2), 124.8 (2C), 127.6 (2C), 134.1, 153.9, 164.8 (C-6), 167.1 (C-2), 169.6 (C-4). Anal. Calcd for $C_{17}H_{23}N_5O$: C, 65.15; H, 7.40; N, 22.35. Found: C, 65.02; H, 7.53; N, 22.23.

*4-(4-(N,N-Dimethylamino)phenyl)-6-morpholino-1,3,5-triazin-2-amine (**1h**).*

Yellow solid; yield 132 mg (18%); mp 209-210 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.99 (Me), 3.62-3.65 (4H, *m*, CH_2OCH_2), 3.76 (4H, *br s*, CH_2NCH_2), 6.71 (2H, *br s*, NH_2), 6.72 (2H, *d*, *J* =9.1 Hz, H-3′ and H-5′), 8.14 (2H, *d*, *J* = 9.0 Hz, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 39.6 ($N(Me)_2$), 43.0 (CH_2NCH_2), 65.9 (CH_2OCH_2), 110.8 (2C), 123.6, 129.1 (2C), 152.3, 164.8 (C-6), 166.9 (C-2), 169.6 (C-4). Anal. Calcd for $C_{15}H_{20}N_6O$: C, 59.98; H, 6.71; N, 27.98. Found: C, 59.87; H, 6.82; N, 27.85.

*4-(4-Methoxyphenyl)-6-morpholino-1,3,5-triazin-2-amine (**1i**).*

Yellowish solid; yield 325 mg (45%); mp 182-183 °C (EtOH), lit.[38] 177-179 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.64-3.68 (4H, *m*, CH_2OCH_2), 3.80 (4H, *br s*, CH_2NCH_2), 3.83 (3H, *s*, OMe), 6.88 (2H, *br s*, NH_2), 7.02 (2H, *d*, *J* = 9.0 Hz, H-3′ and H-5′), 8.28 (2H, *d*, *J* = 9.0 Hz, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2NCH_2), 55.2 (OMe), 66.0 (CH_2OCH_2), 113.4 (2C), 129.2, 129.5 (2C), 161.8, 164.9 (C-6), 167.1 (C-2), 169.3 (C-4). Anal. Calcd for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96; N, 24.38. Found: C, 58.39; H, 6.08; N, 24.23.

*4-(4-(Trifluoromethoxy)phenyl)-6-morpholino-1,3,5-triazin-2-amine (**1j**).*

White solid; yield 220 mg (26%); mp 141-142 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.64-3.67 (4H, *m*, CH_2OCH_2), 3.79 (4H, *br s*, CH_2NCH_2), 7.04 (2H, *br s*, NH_2), 7.46 (2H, *d*, *J* = 8.9 Hz, H-3′ and H-5′), 8.40 (2H, *d*, *J* = 8.9 Hz, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2NCH_2), 65.9 (CH_2OCH_2), 119.9 (*q*, *J* = 257.4 Hz, OCF_3), 120.4 (2C), 129.8 (2C), 136.0, 150.4 (*q*, *J* = 1.5 Hz), 164.8 (C-6), 167.1 (C-2), 168.5 (C-4). Anal. Calcd for $C_{14}H_{14}F_3N_5O_2$: C, 49.27; H, 4.13; N, 20.52. Found: C, 49.13; H, 4.29; N, 20.40.

*6-Morpholino-4-(3-phenoxyphenyl)-1,3,5-triazin-2-amine (**1k**).*

White solid; yield 480 mg (55%); mp 147-148 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.62-3.65 (4H, *m*, CH_2OCH_2), 3.76 (4H, *br s*, CH_2NCH_2), 6.95 (2H, *br s*, NH_2), 7.04 (2H, *m*, H-6″ and H-2″), 7.13-7.22 (2H, *m*, H-4′ and H-4″), 7.37-7.45 (2H, *m*, H-3″ and H-5″), 7.49 (1H, *t*, *J* = 7.9 Hz, H-5′), 7.90 (1H, *dd*, *J* = 1.4, 2.5 Hz, H-2′), 8.09 (1H, *ddd*, *J* = 1.2, 1.4, 7.8 Hz, H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2NCH_2), 65.9 (CH_2OCH_2), 117.7 (C-2′), 118.4 (2C), 121.6, 122.9, 123.4, 129.8, 130.0 (2C), 139.0, 156.5, 156.7, 164.8 (C-6), 167.1 (C-2), 169.0 (C-4). Anal. Calcd for $C_{19}H_{19}N_5O_2$: C, 65.32; H, 5.48; N, 20.04. Found: C, 65.19; H, 5.63; N, 19.88.

*4-(3-(Benzyloxy)phenyl)-6-morpholino-1,3,5-triazin-2-amine (**1l**).*

Light brown solid; yield 362 mg (40%); mp 161-162 °C (MeCN). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.60-3.69 (4H, *m*, CH_2OCH_2), 3.78 (4H, *br s*, CH_2NCH_2), 5.17 (2H, *s*, O*C*H_2Ph), 6.97 (2H, *br s*, NH_2), 7.18 (1H, *ddd*, *J* = 1.0, 2.6, 8.2 Hz, H-4′), 7.30-7.44 (4H, *m*, H-5′, H-3″, H-4″ and H-5″), 7.46-7.51 (2H, *m*, H-2″ and H-6″), 7.88-7.96 (2H, *m*, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2NCH_2), 65.9 (CH_2OCH_2), 69.2 (O*C*H_2Ph), 113.9, 117.7, 120.3, 127.6 (2C), 127.8, 128.4 (2C), 129.2, 137.0, 138.4, 158.2, 164.8 (C-6), 167.1 (C-2), 169.4 (C-4). Anal. Calcd for $C_{20}H_{21}N_5O_2$: C, 66.10; H, 5.82; N, 19.27. Found: C, 65.89; H, 5.96; N, 19.11.

*4-(4-(Benzyloxy)phenyl)-6-morpholino-1,3,5-triazin-2-amine (**1m**).*

Yellow solid; yield 641 mg (71%); mp 164-165 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.61-3.66 (4H, *m*, CH_2OCH_2), 3.78 (4H, *br s*, CH_2NCH_2), 5.17 (2H, *s*, O*C*H_2Ph), 6.86 (2H, *br s*, NH_2), 7.09 (2H, *d*, *J* = 9.0 Hz, H-3′ and H-5′), 7.31-7.51 (5H, *m*, OCH_2*Ph*), 8.25 (2H, *d*, *J* = 8.9 Hz, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2NCH_2), 65.9 (CH_2OCH_2), 69.3 (O*C*H_2Ph), 114.2 (2C), 127.7 (2C), 127.8, 128.4 (2C), 129.3, 129.5 (2C), 136.7, 160.9, 164.8 (C-6), 167.0 (C-2), 169.2 (C-4). Anal. Calcd for $C_{20}H_{21}N_5O_2$: C, 66.10; H, 5.82; N, 19.27. Found: C, 65.98; H, 5.90; N, 19.13.

*4-(3,4-Dimethoxyphenyl)-6-morpholino-1,3,5-triazin-2-amine (**1n**).*

White solid; yield 297 mg (37%); mp 172-173 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.63-3.67 (4H, *m*, CH_2OCH_2), 3.78 (4H, *br s*, CH_2NCH_2), 3.81 (3H, *s*, OMe), 3.82 (3H, *s*, OMe), 6.87 (2H, *br s*, NH_2), 7.03 (1H, *d*, *J* = 8.6 Hz, H-5′), 7.85 (1H, *d*, *J* = 2.0 Hz, H-2′), 7.93 (1H, *dd*, *J* = 2.0, 8.5 Hz, H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2NCH_2), 55.3 (OMe), 55.4 (OMe), 65.9 (CH_2OCH_2), 110.7, 110.9, 121.3, 129.2, 148.1, 151.5, 164.8 (C-6), 167.0 (C-2), 169.3 (C-4). Anal. Calcd for $C_{15}H_{19}N_5O_3$: C, 56.77; H, 6.03; N, 22.07. Found: C, 56.69; H, 6.10; N, 21.98.

*4-(3,4,5-Trimethoxyphenyl)-6-morpholino-1,3,5-triazin-2-amine (**1o**).*

White solid; yield 358 mg (41%); mp 234-235 °C (EtOH), lit.[39] 240 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.64-3.67 (4H, *m*, CH_2OCH_2), 3.73 (3H, *s*, OMe), 3.77 (4H, *br s*, CH_2NCH_2), 3.84 (6H, *s*, 2 x OMe), 6.94 (2H, *br s*, NH_2), 7.62 (2H, *s*, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.1 (CH_2NCH_2), 55.8 (2 x OMe), 60.0 (OMe), 65.9 (CH_2OCH_2), 105.0 (2C), 132.2, 140.3, 152.5 (2C), 164.8 (C-6), 167.0 (C-2), 169.2 (C-4). Anal. Calcd for $C_{16}H_{21}N_5O_4$: C, 55.32; H, 6.09; N, 20.16. Found: C, 55.23; H, 6.22; N, 19.99.

*6-Morpholino-4-(thiophen-2-yl)-1,3,5-triazin-2-amine (**1p**).*

Light brown solid; yield 352 mg (53%); mp 145-146 °C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.62-3.66 (4H, *m*, CH_2OCH_2), 3.75 (4H, *br s*, CH_2NCH_2), 6.96 (2H, *br s*, NH_2), 7.16 (1H, *dd*, *J* = 3.7, 5.0 Hz, H-4′), 7.73 (1H, *dd*, *J* = 1.3, 5.0 Hz, H-5′), 7.88 (1H, *dd*, *J* = 1.2, 3.7 Hz, H-3′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 43.0 (CH_2NCH_2), 65.9 (CH_2OCH_2), 127.9, 129.1, 130.6, 142.7, 164.4 (C-6), 166.1 (C-2), 166.8 (C-4). Anal. Calcd for $C_{11}H_{13}N_5OS$: C, 50.18; H, 4.98; N, 26.60. Found: C, 50.06; H, 5.07; N, 26.39.

*6-Phenyl-4-pyrrolidino-1,3,5-triazin-2-amine (**1q**).*

White solid; yield 87 mg (14%); mp 230-231 °C (EtOH), lit.[24] 230 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.88-1.94 (4H, *m*, CH_2CH_2), 3.44-3.50 (2H, *m*, CH_2NCH_2), 3.58-3.64 (2H, *m*, CH_2NCH_2), 6.82 (2H, *br s*, NH_2), 7.42-7.54 (3H, *m*, H-3′, H-4′, and H-5′), 8.27-8.32 (2H, *m*, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.65 (CH_2), 24.73 (CH_2), 45.6 (CH_2N), 45.8 (CH_2N), 127.6 (2C), 128.0 (2C), 130.9, 137.1, 163.5 (C-6), 166.9 (C-2), 169.1 (C-4). Anal. Calcd for $C_{13}H_{15}N_5$: C, 64.71; H, 6.27; N, 29.02. Found: C, 64.55; H, 6.47; N, 28.90.

*6-Phenyl-4-piperidino-1,3,5-triazin-2-amine (**1r**).*

White solid; yield 61 mg (10%); mp 146-147 °C (EtOH), lit.[40] 149-151 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.46-1.55 (4H, *m*, $CH_2CH_2CH_2$), 1.59-1.66 (4H, *m*, $CH_2CH_2CH_2$), 3.80 (4H, *br s*, CH_2NCH_2), 6.84 (2H, *br s*, NH_2), 7.42-7.53 (3H, *m*, H-3′, H-4′, and H-5′), 8.26-8.31 (2H, *m*, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.2 (CH_2), 25.3 (2 x CH_2), 43.4 (CH_2NCH_2), 127.6 (2C), 128.0 (2C), 131.0, 137.1, 164.5 (C-6), 167.2 (C-2), 169.5 (C-4). Anal. Calcd for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43. Found: C, 65.73; H, 6.85; N, 27.28.

*4-(4-Methylpiperidino)-6-phenyl-1,3,5-triazin-2-amine (**1s**).*

White solid; yield 58 mg (9%); mp >300°C (EtOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.93 (3H, *d*, *J* = 6.3 Hz, Me), 1.00-1.11 (2H, *m*, C*H*$_2$CHMeC*H*$_2$-ax), 1.61-1.71 (3H, *m*, C*H*Me, C*H*$_2$NC*H*$_2$-ax), 2.86 (2H, *br t*, *J* = 12.2 Hz, C*H*$_2$CHMeC*H*$_2$-eq), 4.72 (1H, *br s*, NC*H*$_2$-eq), 4.81 (1H, *br s*, NC*H*$_2$-eq), 6.85 (2H, *br s*, NH_2), 7.42-7.53 (3H, *m*, H-3′, H-4′, and H-5′), 8.26-8.31 (2H, *m*, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.7 (Me), 30.6 (2 x CH_2), 33.5 (*C*HMe), 42.7 (CH_2NCH_2), 127.6 (2C), 128.0 (2C), 131.0, 137.1, 164.5 (C-6), 167.2 (C-2), 169.6 (C-4). Anal. Calcd for $C_{15}H_{19}N_5$: C, 66.89; H, 7.11; N, 26.00. Found: C, 66.78; H, 7.23; N, 25.83.

*4-(4-Methylpiperazino)-6-phenyl-1,3,5-triazin-2-amine (**1t**).*

Yield 231 mg (34%); mp 173-174 °C (EtOH), lit.[22] 171-174 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.21 (3H, *s*, NMe), 2.32-2.38 (4H, *m*,

$CH_2N(Me)CH_2$), 3.81 (4H, *br s*, CH_2NCH_2), 6.92 (2H, *br s*, NH_2), 7.42-7.55 (3H, *m*, H-3′, H-4′, and H-5′), 8.26-8.31 (2H, *m*, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 42.4 (NMe), 45.7 (CH_2NCH_2), 54.3 ($CH_2N(Me)CH_2$), 127.7 (2C), 128.1 (2C), 131.1, 136.9, 164.7 (C-6), 167.1 (C-2), 169.6 (C-4). Anal. Calcd for $C_{14}H_{18}N_6$: C, 62.20; H, 6.71; N, 31.09. Found: C, 62.07; H, 6.82; N, 30.92.

*4-(3,4-Dihydroisoquinolin-2(1H)-yl)-6-phenyl-1,3,5-triazin-2-amine (**1u**).*

Yellowish solid; yield 290 mg (38%); mp 139-140 °C (EtOH). ^1H NMR (300 MHz, DMSO-d_6): δ 2.88 (2H, *br t*, *J* = 6.0 Hz, NCH_2CH_2), 4.01 (1H, *br s*, NCH_2CH_2), 4.11 (1H, *br s*, NCH_2CH_2), 4.89 (1H, *br s*, NCH_2Ar), 5.02 (1H, *br s*, NCH_2Ar), 6.96 (2H, *br s*, NH_2), 7.18-7.32 (4H, *m*, NCH_2ArCH_2), 7.45-7.58 (3H, *m*, H-3′, H-4′, and H-5′), 8.32-8.37 (2H, *m*, H-2′ and H-6′). ^{13}C NMR (75 MHz, DMSO-d_6): δ 28.4 (NCH_2CH_2), 40.4 (NCH_2CH_2), 44.9 (NCH_2Ar), 126.0, 126.2, 126.3, 127.7 (2C), 128.1 (2C), 131.1, 133.7 (*br s*), 134.7, 136.9, 164.8 (C-6), 167.1 (C-2), 169.6 (C-4). Anal. Calcd for $C_{18}H_{17}N_5$: C, 71.27; H, 5.65; N, 23.09. Found: C, 71.17; H, 5.76; N, 22.91.

X-ray crystal structure determination

Intensity data for **1l** and **1n** were measured for colourless crystals (**11**: 0.07 × 0.17 × 0.19 mm; **1m**: 0.10 × 0.15 × 0.18 mm) at 100 K on an Rigaku/Oxford Diffraction XtaLAB Synergy diffractometer (Dualflex, AtlasS2) fitted with CuKα radiation (λ = 1.54178 Å) so that θ(100% data completeness) = 67.1 and 67.7°, respectively. Data reduction and Gaussian absorption corrections were by standard methods.[41] The structures were solved by direct methods[42] and refined (anisotropic displacement parameters and with C-bound H atoms included in the riding model approximation) on F^2.[43] The N-bound H atoms were refined with N–H = 0.88 ± 0.01 Å. A weighting scheme of the form w = $1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, where $P = (F_o^2 + 2F_c^2)/3$), was introduced in each case. The molecular structure diagrams showing 70% probability displacement ellipsoids were generated by ORTEP for Windows[44] and the packing diagrams with DIAMOND.[45] Additional data analysis was made with PLATON.[46]

*Crystal data for **1l**.* $C_{20}H_{21}N_5O_2$, *M* = 363.42, triclinic, *P*$\bar{1}$, *a* = 5.32441(9), *b* = 9.52388(12), *c* = 17.7526(3) Å, α = 90.2806(12), β = 97.7765(14), γ = 91.0148(12)°, *V* = 891.77(2) Å^3, *Z* = 2, D_x = 1.353 g cm^{-3}, *F*(000) = 384, μ = 0.737 mm^{-1}, no. reflns meas. = 21209, no. unique reflns = 3185 (R_{int} = 0.020), no. reflns with $I \geq 2\sigma(I)$ = 3083, no. parameters = 250, *R*(obs. data) = 0.033, *a* and *b* in weighting scheme = 0.051 and 0.256, *wR*2(all data) = 0.090. CCDC deposition number: 2035574.

*Crystal data for **1n**.* $C_{15}H_{19}N_5O_3$, *M* = 317.35, monoclinic, $P2_1/c$, *a* = 8.2512(2), *b* = 14.9301(4), *c* = 12.1258(3) Å, β = 99.743(3)°, *V* = 1472.25(7) Å^3, *Z* = 4, D_x = 1.432 g cm^{-3}, *F*(000) = 672, μ = 0.853 mm^{-1}, no. reflns meas. = 19752, no. unique reflns = 3045 (R_{int} = 0.042), no. reflns with $I \geq 2\sigma(I)$ = 2746, no. parameters = 216, *R*(obs. data) = 0.042, *a* and *b* in weighting scheme = 0.078 and 0.443, *wR*2(all data) = 0.126. CCDC deposition number: 2035575.

Antiproliferative activity screening

The Jurkat-T cells (human leukemic T cell, clone E6-1) from American Type Culture Collection (ATCC) were cultured in RPM1-1640 medium (Nacalai Tesque, Japan) supplemented with 10% v/v foetal bovine serum (FBS) (Biosera, France) and maintained at 37 °C in a humidified 5% CO_2 incubator (Thermo Fisher, USA). The MTS assay[47] was used in the cell viability experiments. A total of 2 × 10^4 cells in 50 μL cell culture media were seeded into each well of a 96-well plate and incubated for 24 h. Then, tested compounds or reference drugs [6-mercaptopurine (Merck Millipore, Germany), methotrexate (Merck Millipore, Germany), and cytarabine (Merck Millipore, Germany)] were added followed by the incubation for 72 h. After that, a mixture of 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium inner salt (MTS) (Sigma Aldrich, USA) and phenazine methosulfate (Nacalai Tesque, Japan) was added to each well, followed by another incubation for 1-4 h at 37 ºC. The absorbance in each well was measured at 490 nm using a microplate reader (Tecan NanoQuant Infinite M200 Pro, Austria). The percentage of cell viability was estimated by comparing absorbance in wells with the treated and untreated (vehicle control) cells using the following formula: $OD_{treated}/OD_{untreated}$ x 100%. All experiments were done in triplicates and repeated in three independent experiments. The GI_{50} values were calculated using sigmoidal concentration-response curves generated by the GraphPad Prism 8 program.[48]

Funding Information

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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Synthesis

Supporting Information

A new one-pot three-component synthesis of 4-aryl-6-cycloamino-1,3,5-triazin-2-amines under microwave irradiation

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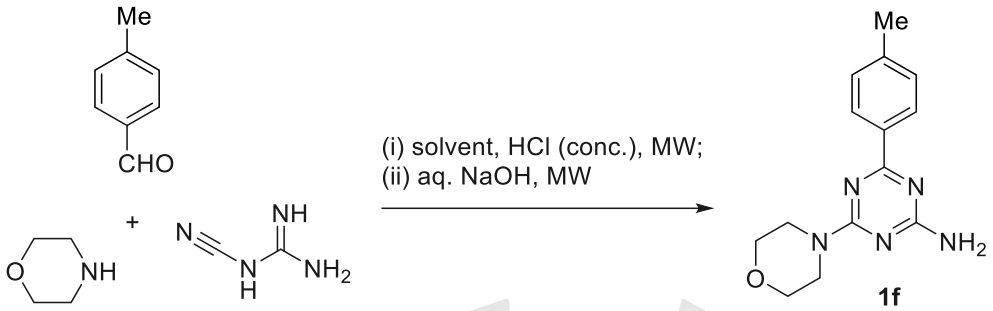
Contents

Table S1. Optimization of reaction conditions for the synthesis of 4-(4-methylphenyl)-6-morpholino-1,3,5-triazin-2-amine (**1f**) under microwave irradiation.[a]



Entry	Solvent	Temperature, °C	Reaction time, min		Yield,[b] %
			(i)	(ii)	
1	MeOH	140	20	15	33
2	EtOH	140	20	15	37
3	PrOH	140	20	15	9
4	EtOH	130	20	15	28
5	EtOH	150	20	15	31
6	EtOH	140	15	15	20
7	EtOH	140	30	15	38
8	EtOH	140	40	15	40
9	EtOH	140	50	15	39
10	EtOH	140	55	15	44
11	EtOH	140	60	15	39
12	EtOH	140	55	5	39
13	EtOH	140	55	10	43
14	EtOH	140	55	20	48
15	EtOH	140	55	25	46
16	EtOH	140	55	60	41
17[c]	EtOH	140	55	20	33
18[d]	EtOH	140	55	20	26
19[e]	EtOH	140	55	20	6
20[f]	EtOH	140	55	20	33

[a] The reactions were performed in a Monowave 400 microwave reactor (Anton Paar, Austria) using cyanoguanidine (2.5 mmol), *p*-tolualdehyde (2.5 mmol), morpholine (2.5 mmol), and conc. HCl (2.5 mmol) in 2 mL of the specified solvent in step (i) and addition of 1 mL of 5 N NaOH (aq.) in step (ii).

[b] Isolated yield calculated on the basis of cyanoguanidine.

[c] The reaction was carried out using 5 mmol of *p*-tolualdehyde.

[d] Another 2.5 mmol of *p*-tolualdehyde was added to the reaction mixture in step (ii).

[e] 0.5 mL of 5 N NaOH (aq.) [2.5 mmol] was used in step (ii).

[f] The reaction was performed in a Monowave 50 reactor (Anton Paar, Austria) without microwave irradiation.

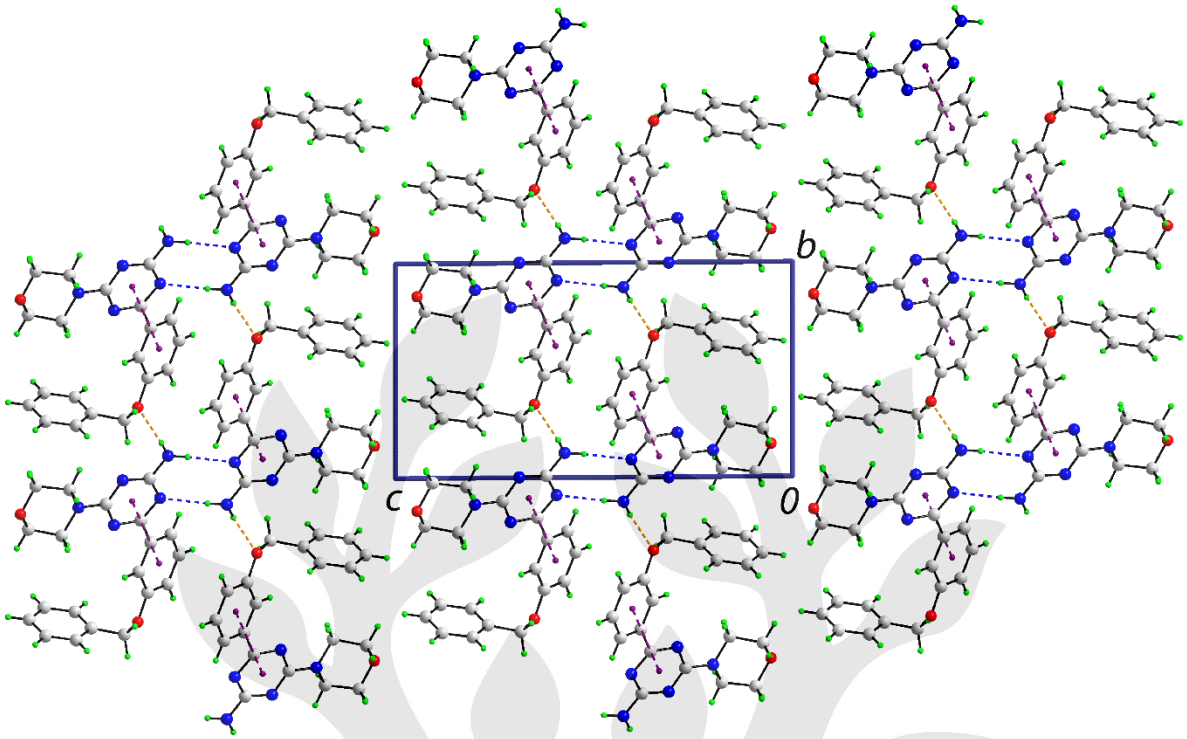


Figure S1. Molecular packing in **1l**: a view in projection down the a-axis of the unit cell contents. The N–H···O, N–H···N, and π···π interactions are shown as orange, blue, and purple dashed lines, respectively.

Geometric parameters (Å, °) characterising the identified intermolecular interactions:

A	H	B	A–H	H···B	A···B	A–H···B	symmetry operation
N2	H1n	N3	0.893(9)	2.129(9)	3.0160(12)	172.2(10)	1-*x*, 2-*y*, 1-*z*
N2	H2n	O1	0.879(11)	2.138(12)	2.9903(11)	163.4(10)	1+*x*, 1+*y*, *z*
Cg(N1-N3,C2,C4,C6)							
		Cg(C41-C46)			3.8674(6)	26.77(5)	1+*x*, *y*, *z*

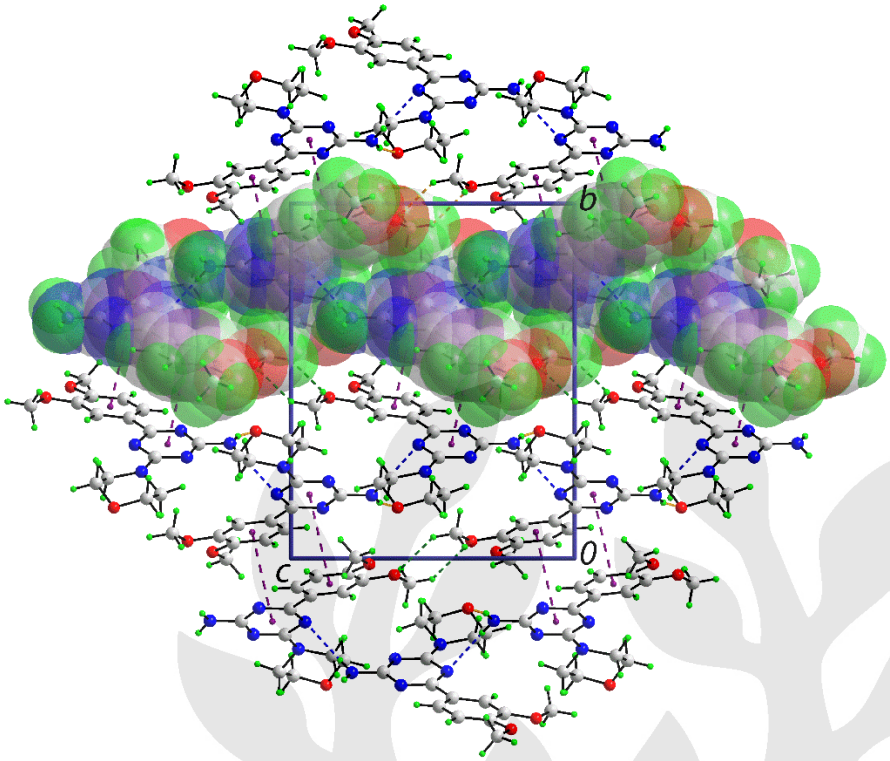


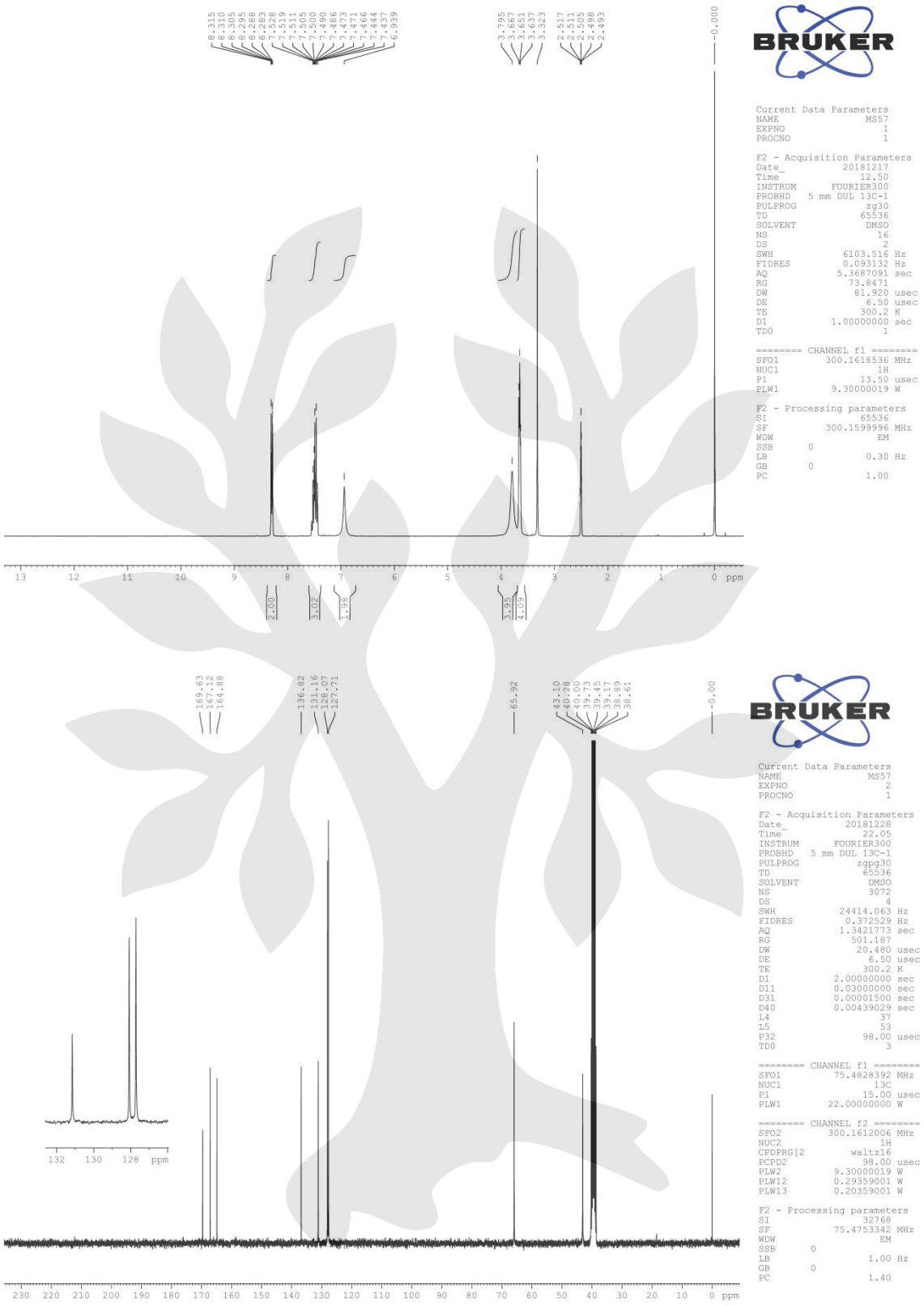
Figure S2. Molecular packing in **1n**: a view in projection down the a-axis of the unit cell contents. The N–H···O, N–H···N, C–H···O, and π···π interactions are shown as orange, blue, green, and purple dashed lines, respectively. One supramolecular layer is highlighted in space-filling mode.

Geometric parameters (Å, °) characterising the identified intermolecular interactions:

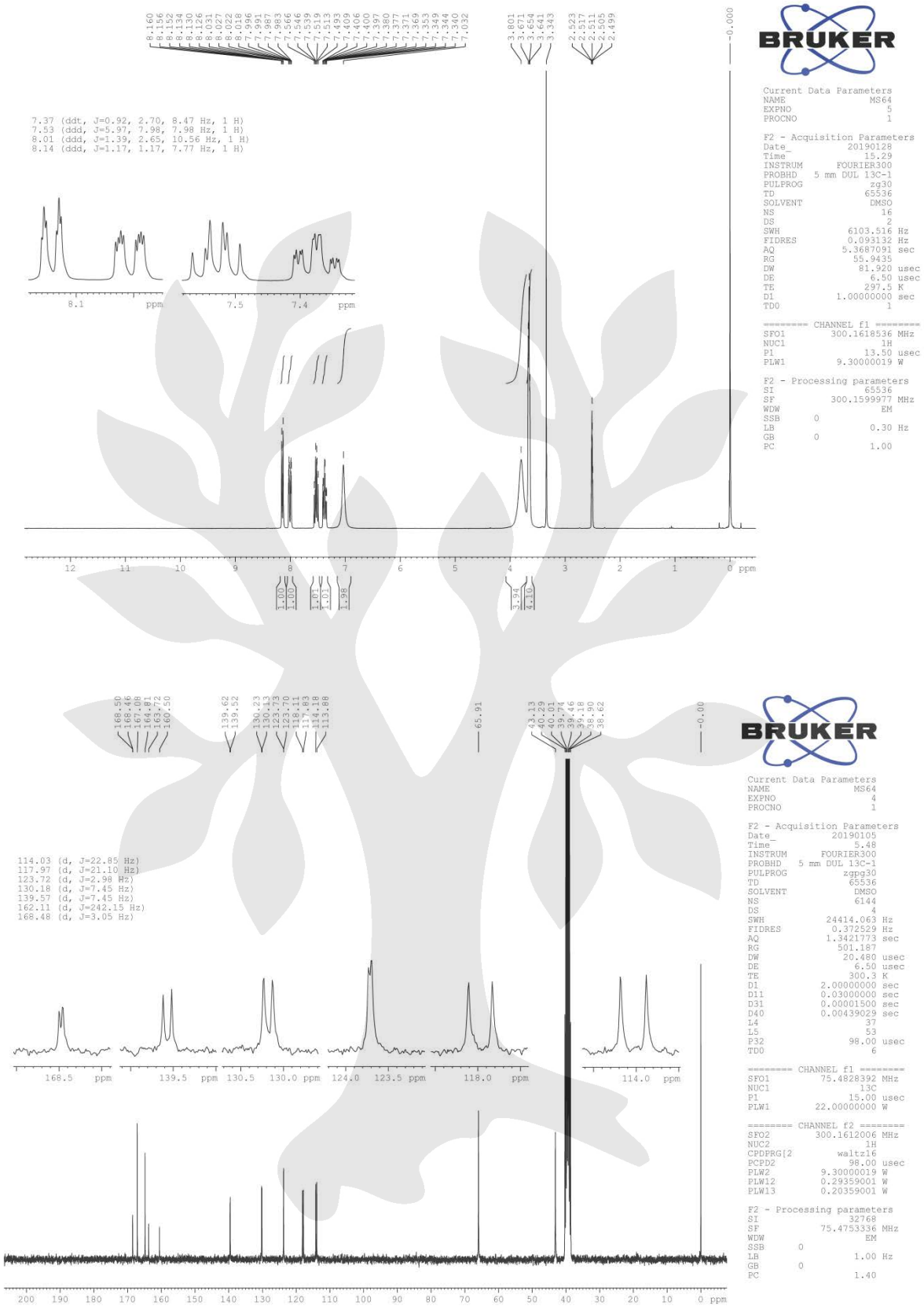
A	H	B	A–H	H···B	A···B	A–H···B	symmetry operation
N2	H1n	O3	0.877(13)	2.108(12)	2.9634(14)	165.0(15)	-1+*x*, ½-*y*, -½+*z*
N2	H2n	N5	0.880(15)	2.381(15)	3.2417(16)	165.8(13)	*x*, ½-*y*, -½+*z*
C62	H62a	O1	0.99	2.39	3.3434(16)	161	1+*x*, ½-*y*, -½+*z*
C47	H47b	O1	0.98	2.53	3.3496(16)	141	-*x*, 1-*y*, 2-*z*
Cg(N1-N3,C2,C4,C6)							
		Cg(C41-C46)			3.8765(7)	11.28(6)	-*x*, 1-*y*, 1-*z*
Cg(N1-N3,C2,C4,C6)							
		Cg(C41-C46)			3.8674(6)	26.77(5)	1+*x*, *y*, *z*

Copies of ^{1}H and ^{13}C NMR spectra for prepared 4-aryl-6-cycloamino-1,3,5-triazin-2-amines (1a-u)

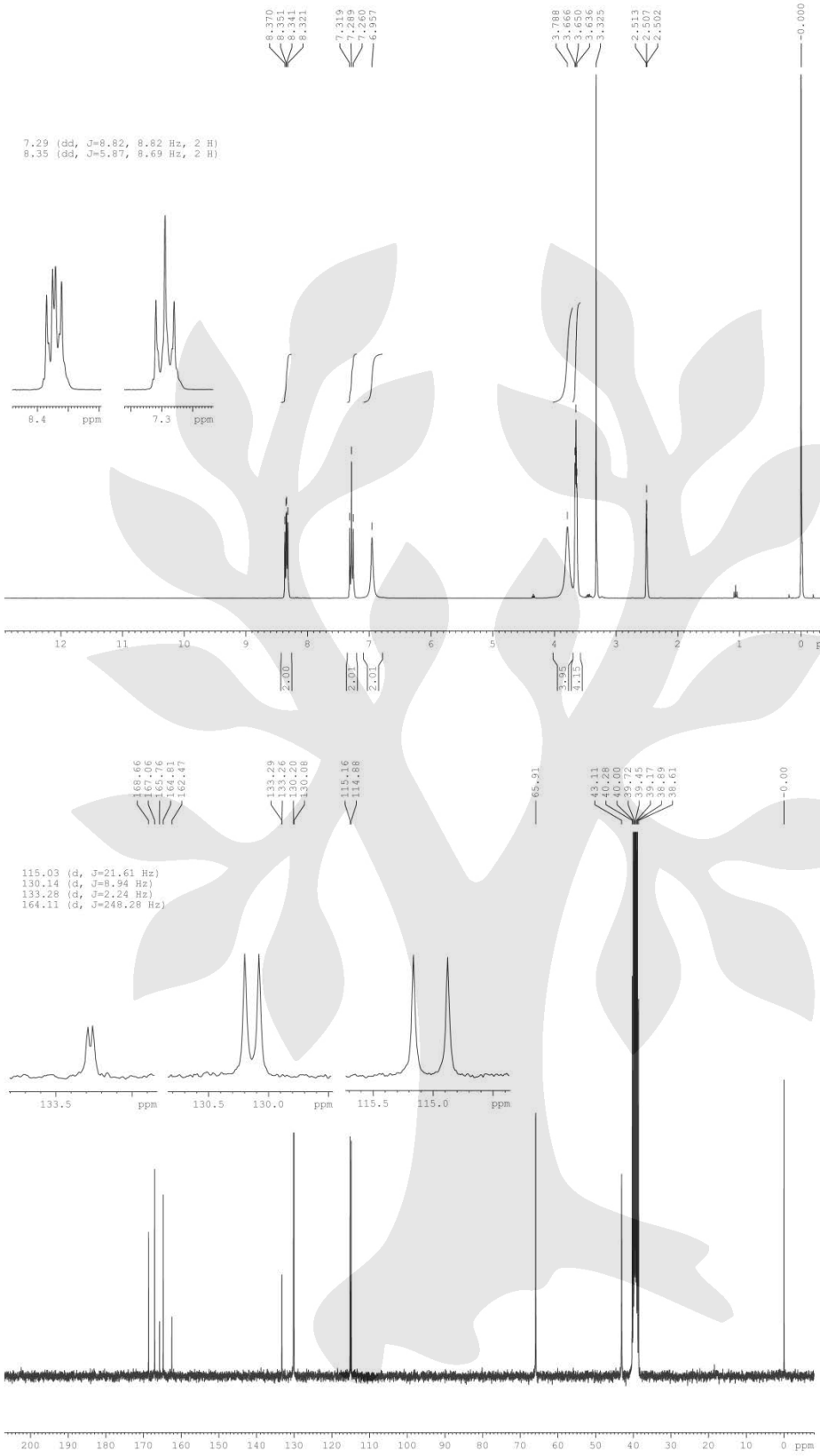
*6-Morpholino-4-phenyl-1,3,5-triazin-2-amine (**1a**).*



*4-(3-Fluorophenyl)-6-morpholino-1,3,5-triazin-2-amine (**1b**).*



*4-(4-Fluorophenyl)-6-morpholino-1,3,5-triazin-2-amine (**1c**).*

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EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20190114
Time_                 12.53
INSTRUM       FOURIER300
PROBHD   5 mm DUL 13C-1
PULPROG               zg30
TD                   65536
SOLVENT               DMSO
NS                      16
DS                       2
SWH               6103.516 Hz
FIDRES            0.093132 Hz
AQ                5.3687091 sec
RG                   74.3131
DW                  81.920 usec
DE                   6.50 usec
TE                  300.1 K
D1              1.00000000 sec
TDO                      1

======== CHANNEL f1 ========
SFO1           300.1618536 MHz
NUC1                    1H
P1                   13.50 usec
PLW1            9.30000019 W

F2 - Processing parameters
SI                   65536
SF             300.1599988 MHz
WDW                     EM
SSB       0
LB                    0.30 Hz
GB        0
PC                    1.00
```

```
Current Data Parameters
NAME                  MS60
EXPNO                    3
PROCNO                   1

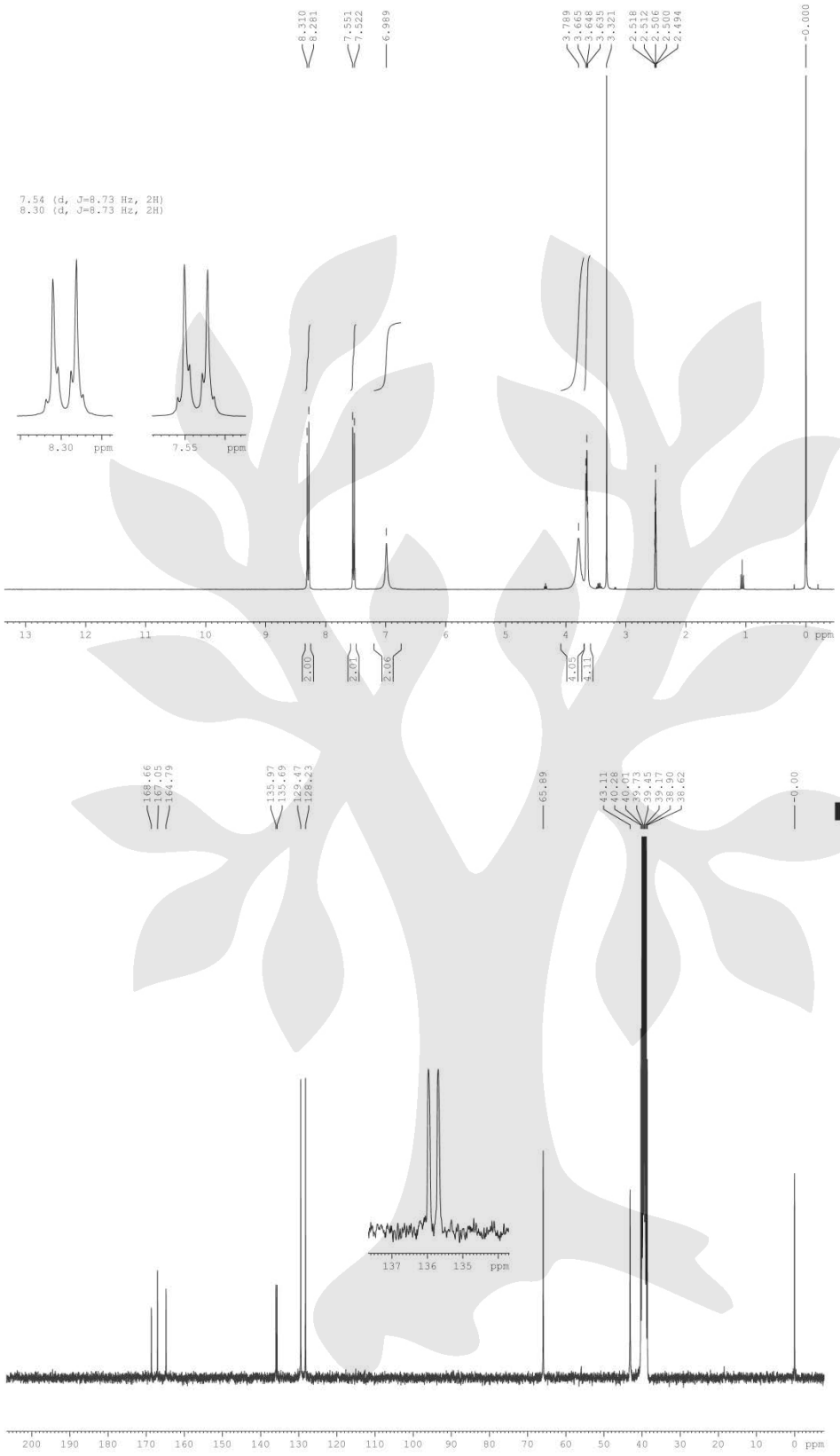
F2 - Acquisition Parameters
Date_              20190117
Time_                 20.13
INSTRUM       FOURIER300
PROBHD   5 mm DUL 13C-1
PULPROG             zgpg30
TD                   65536
SOLVENT               DMSO
NS                    7168
DS                       4
SWH              24414.063 Hz
FIDRES            0.372529 Hz
AQ                1.3421773 sec
RG                  501.187
DW                 20.480 usec
DE                   6.50 usec
TE                  300.3 K
D1              2.00000000 sec
D11             0.03000000 sec
D31             0.00001500 sec
D40             0.00439029 sec
L4                      37
L5                      53
P32                98.00 usec
TDO                      7

======== CHANNEL f1 ========
SFO1            75.4828392 MHz
NUC1                    13C
P1                   15.00 usec
PLW1           22.00000000 W

======== CHANNEL f2 ========
SFO2           300.1612006 MHz
NUC2                    1H
CPDPRG[2            waltz16
PCPD2                98.00 usec
PLW2            9.30000019 W
PLW12           0.29359001 W
PLW13           0.20359001 W

F2 - Processing parameters
SI                   32768
SF              75.4753337 MHz
WDW                     EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    1.40
```

*4-(4-Chlorophenyl)-6-morpholino-1,3,5-triazin-2-amine (**1d**).*

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Current Data Parameters
NAME                  MS84
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20190114
Time                 13.03
INSTRUM         FOURIER300
PROBHD    5 mm DUL 13C-1
PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                     16
DS                      2
SWH             6103.516 Hz
FIDRES             0.093132 Hz
AQ                5.3687091 sec
RG                   81.2426
DW                  81.920 usec
DE                   6.50 usec
TE                  300.2 K
D1                1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1            300.1618536 MHz
NUC1                    1H
P1                   13.50 usec
PLW1             9.30000019 W

F2 - Processing parameters
SI                    65536
SF              300.1599991 MHz
WDW                     EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```
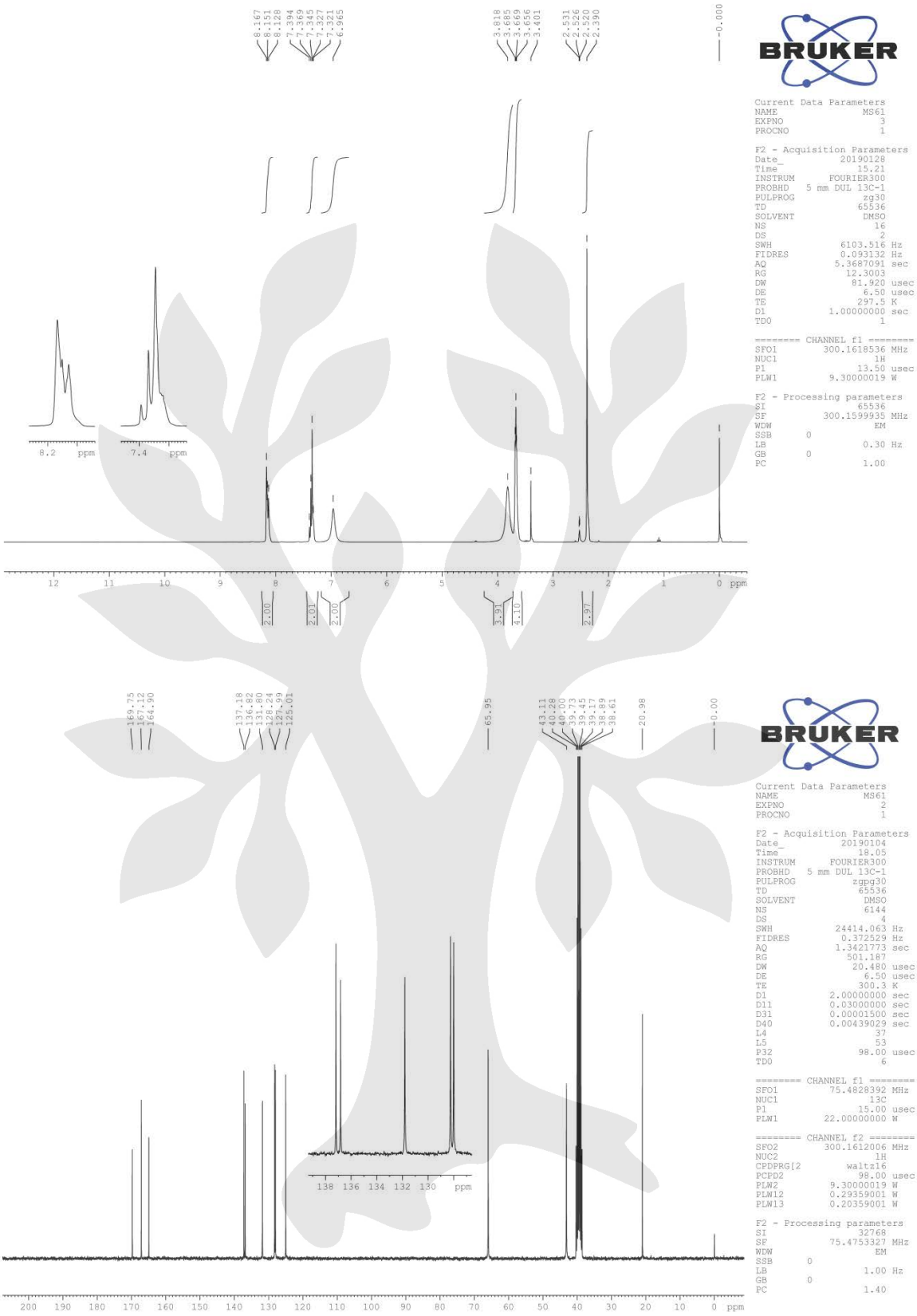
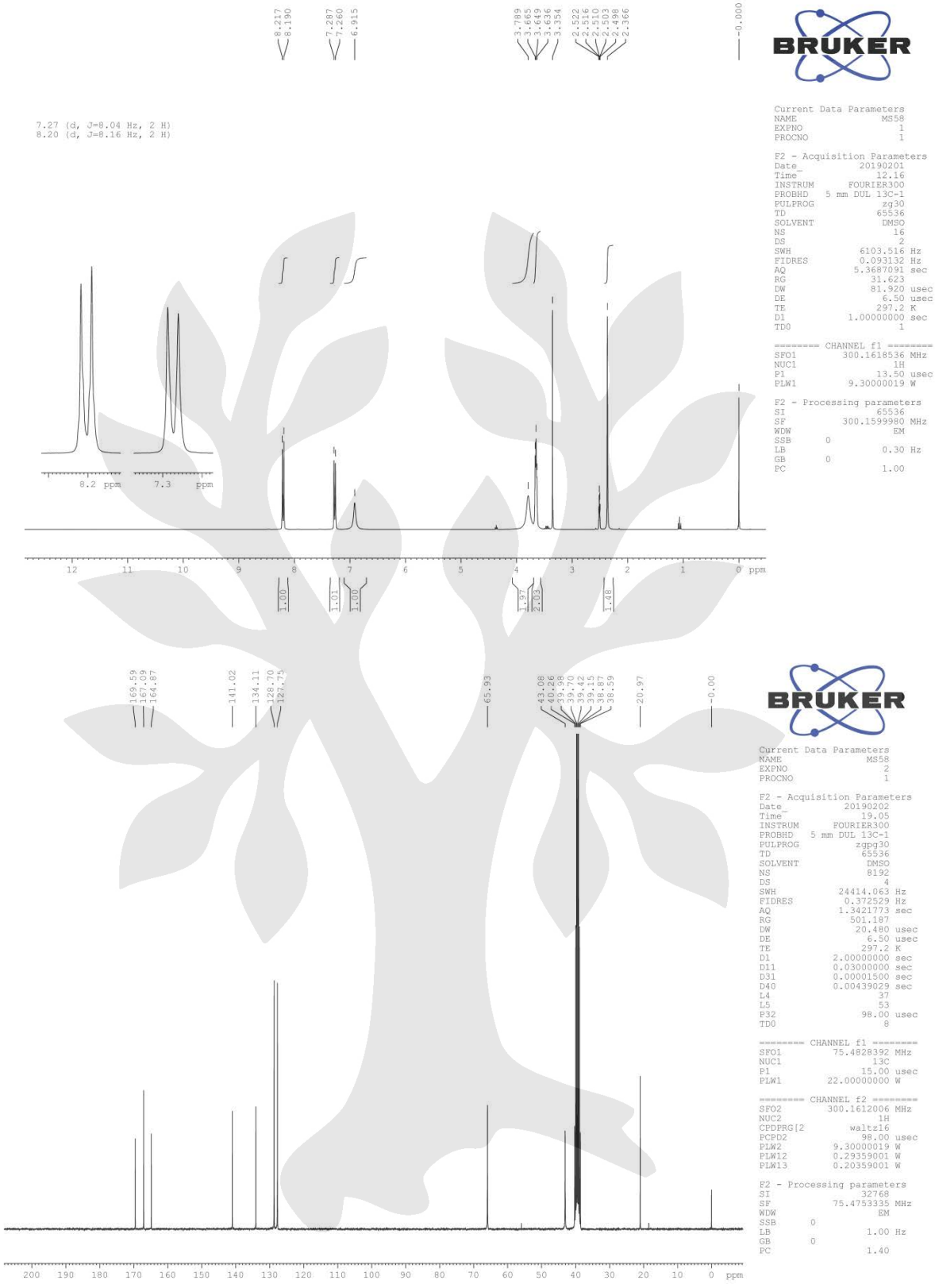

```
Current Data Parameters
NAME                  MS84
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_              20190114
Time                 18.05
INSTRUM         FOURIER300
PROBHD    5 mm DUL 13C-1
PULPROG            zgpg30
TD                  65536
SOLVENT              DMSO
NS                   12288
DS                       4
SWH            24414.063 Hz
FIDRES             0.372529 Hz
AQ                1.3421773 sec
RG                   501.187
DW                  20.480 usec
DE                   6.50 usec
TE                  300.2 K
D1                2.00000000 sec
D11               0.03000000 sec
D31               0.00001500 sec
D40               0.00439029 sec
L4                      37
L5                      53
P32                 98.00 usec
TD0                     12

======== CHANNEL f1 ========
SFO1             75.4828392 MHz
NUC1                    13C
P1                   15.00 usec
PLW1            22.00000000 W

======== CHANNEL f2 ========
SFO2            300.1612006 MHz
NUC2                    1H
CPDPRG[2            waltz16
PCPD2                98.00 usec
PLW2             9.30000019 W
PLW12            0.29359001 W
PLW13            0.20359001 W

F2 - Processing parameters
SI                    32768
SF              75.4753345 MHz
WDW                     EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

*6-Morpholino-4-(3-methylphenyl)-1,3,5-triazin-2-amine (**1e**).*



*4-(4-Methylphenyl)-6-morpholino-1,3,5-triazin-2-amine (**1f**).*



*4-(4-(tert-Butyl)phenyl)-6-morpholino-1,3,5-triazin-2-amine (**1g**).*

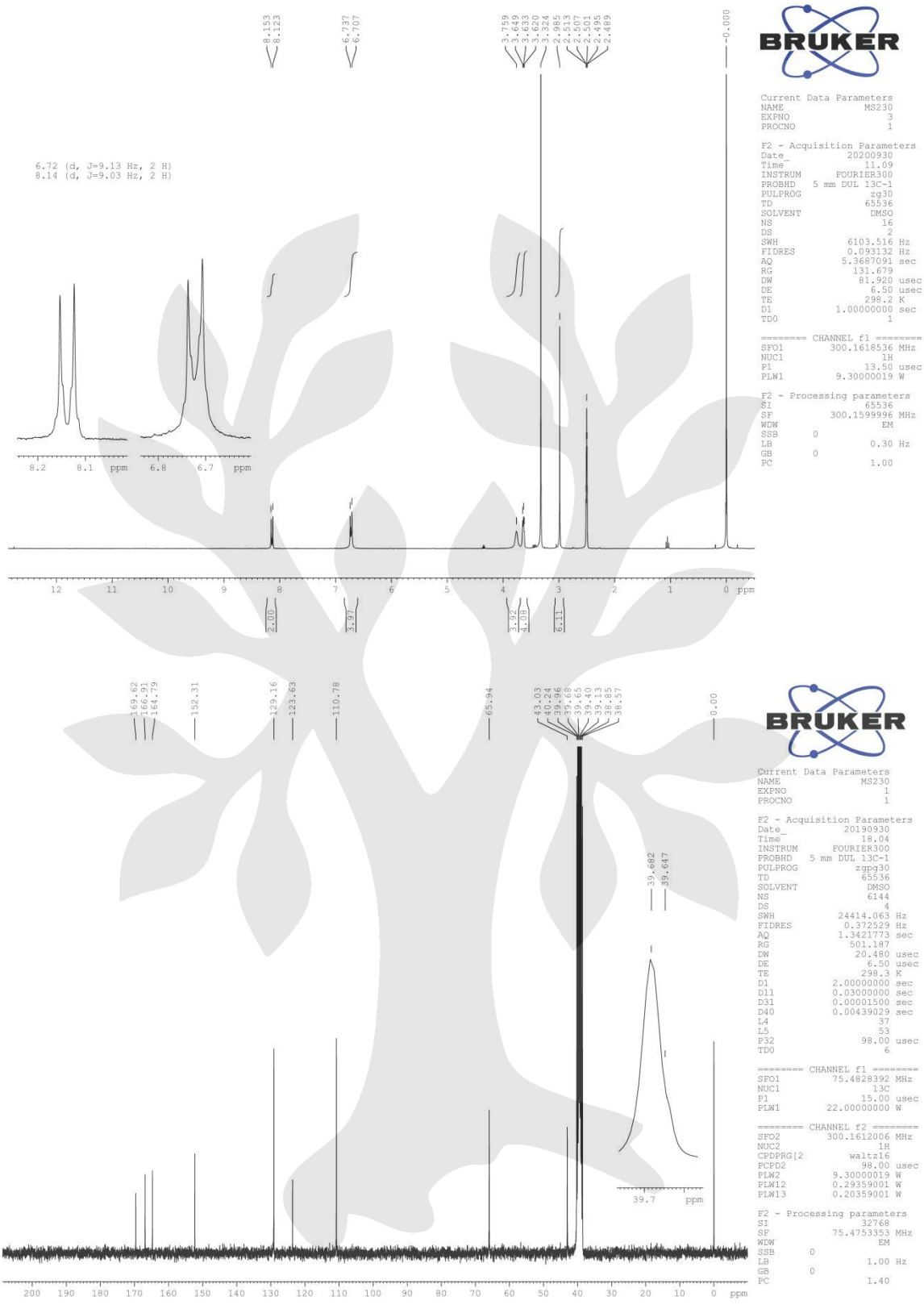
BRUKER

```
Current Data Parameters
NAME                  MS68
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20190627
Time                 13.20
INSTRUM         FOURIER300
PROBHD    5 mm DUL 13C-1
PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                      16
DS                       2
SWH               6103.516 Hz
FIDRES           0.093132 Hz
AQ                5.3687091 sec
RG                   72.6053
DW                 81.920 usec
DE                   6.50 usec
TE                  298.1 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1            300.1618536 MHz
NUC1                    1H
P1                   13.50 usec
PLW1             9.30000019 W

F2 - Processing parameters
SI                      65536
SF              300.1599995 MHz
WDW                     EM
SSB         0
LB                   0.30 Hz
GB          0
PC                   1.00
```

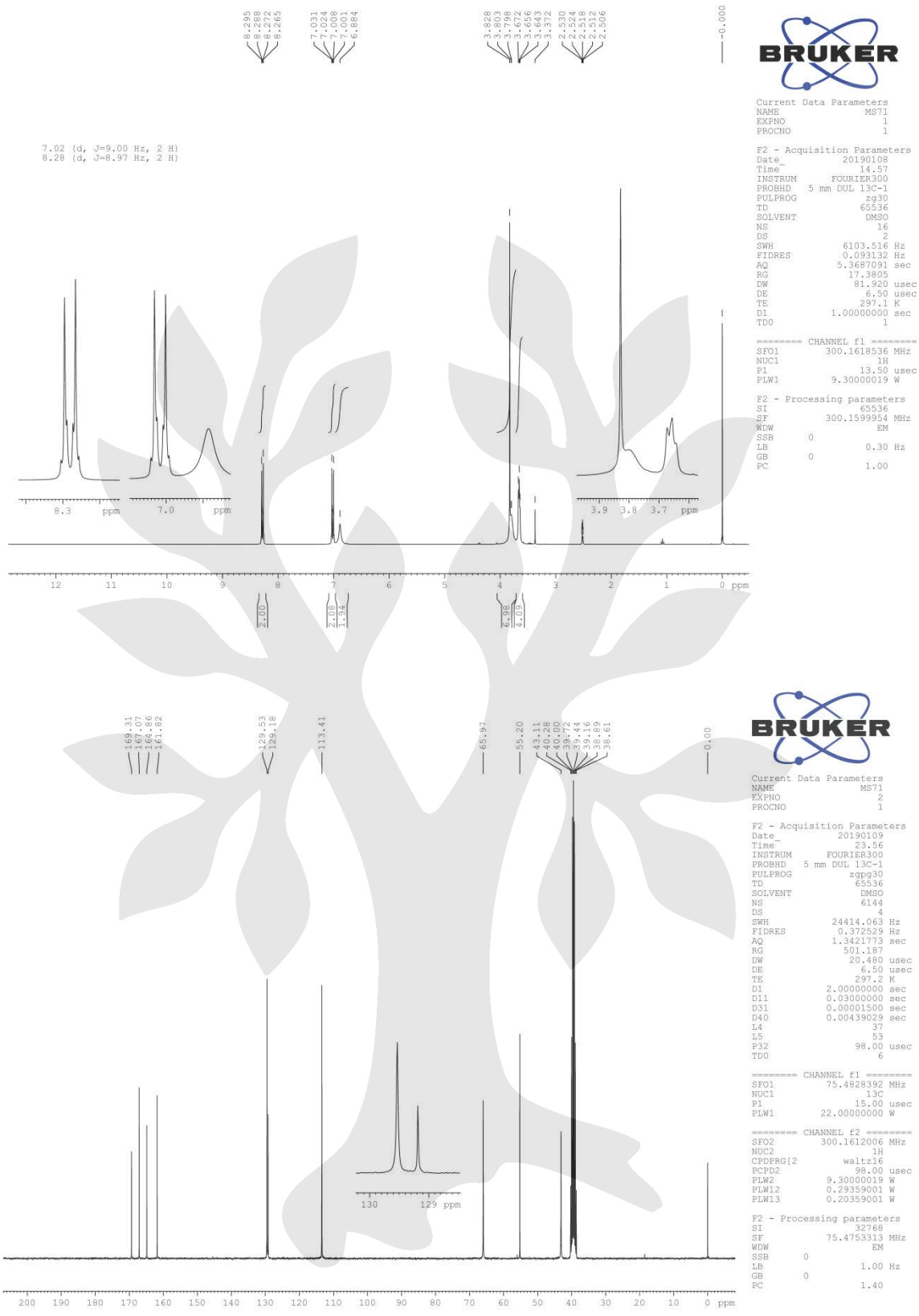
BRUKER

```
Current Data Parameters
NAME                  MS68
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_              20190701
Time                 18.19
INSTRUM         FOURIER300
PROBHD    5 mm DUL 13C-1
PULPROG            zgpg30
TD                  65536
SOLVENT              DMSO
NS                   12288
DS                       4
SWH              24414.063 Hz
FIDRES           0.372529 Hz
AQ                1.3421773 sec
RG                   501.187
DW                 20.480 usec
DE                   6.50 usec
TE                  298.2 K
D1              2.00000000 sec
D11             0.03000000 sec
D31             0.00001500 sec
D40             0.00439029 sec
L4                      37
L5                      53
P32                98.00 usec
TD0                     12

======== CHANNEL f1 ========
SFO1            75.4828392 MHz
NUC1                    13C
P1                   15.00 usec
PLW1           22.00000000 W

======== CHANNEL f2 ========
SFO2           300.1612006 MHz
NUC2                    1H
CPDPRG[2            waltz16
PCPD2                98.00 usec
PLW2            9.30000019 W
PLW12           0.29359001 W
PLW13           0.20359001 W

F2 - Processing parameters
SI                      32768
SF              75.4753365 MHz
WDW                     EM
SSB         0
LB                   1.00 Hz
GB          0
PC                   1.40
```

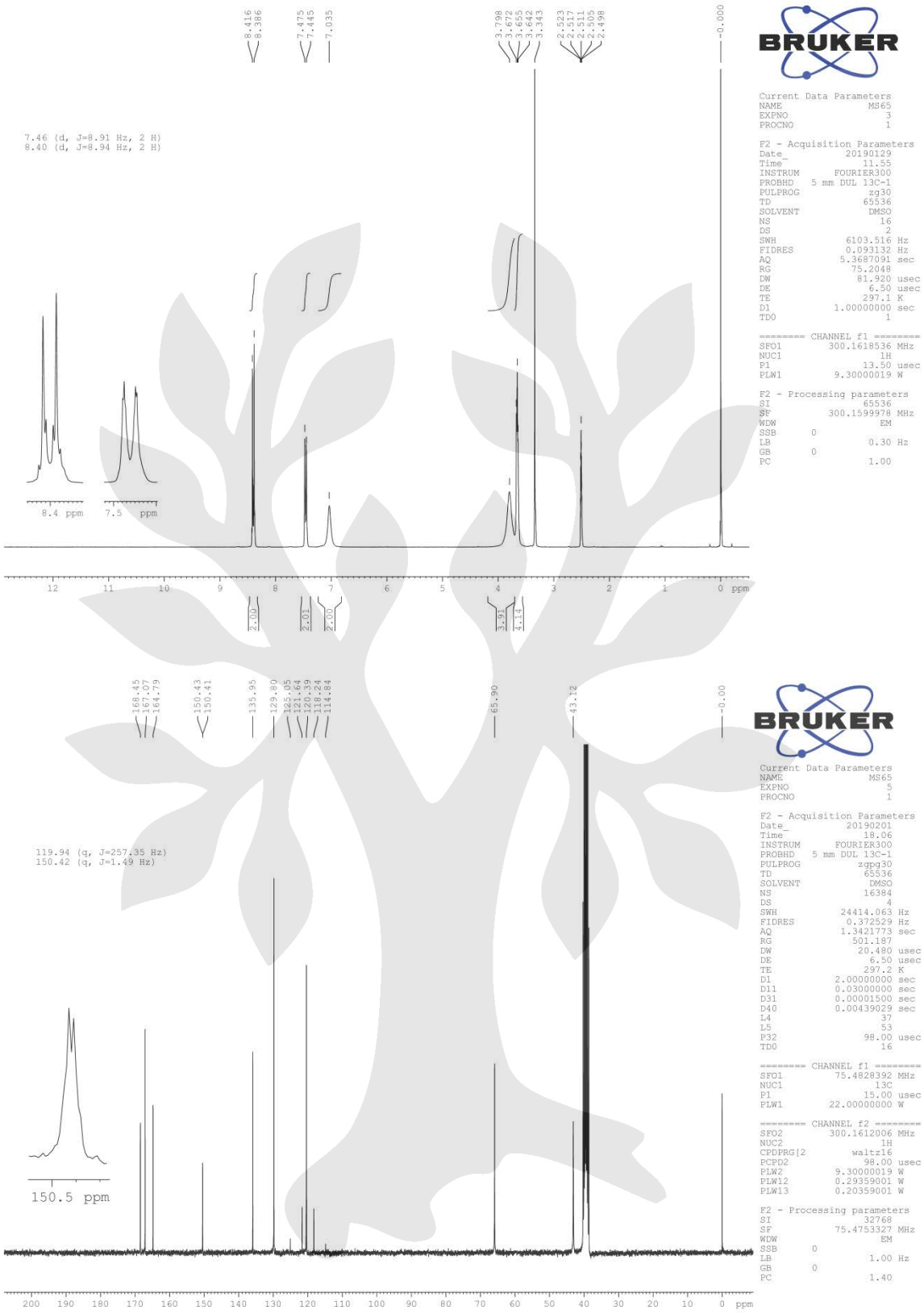
*4-(4-(N,N-Dimethylamino)phenyl)-6-morpholino-1,3,5-triazin-2-amine (**1h**).*



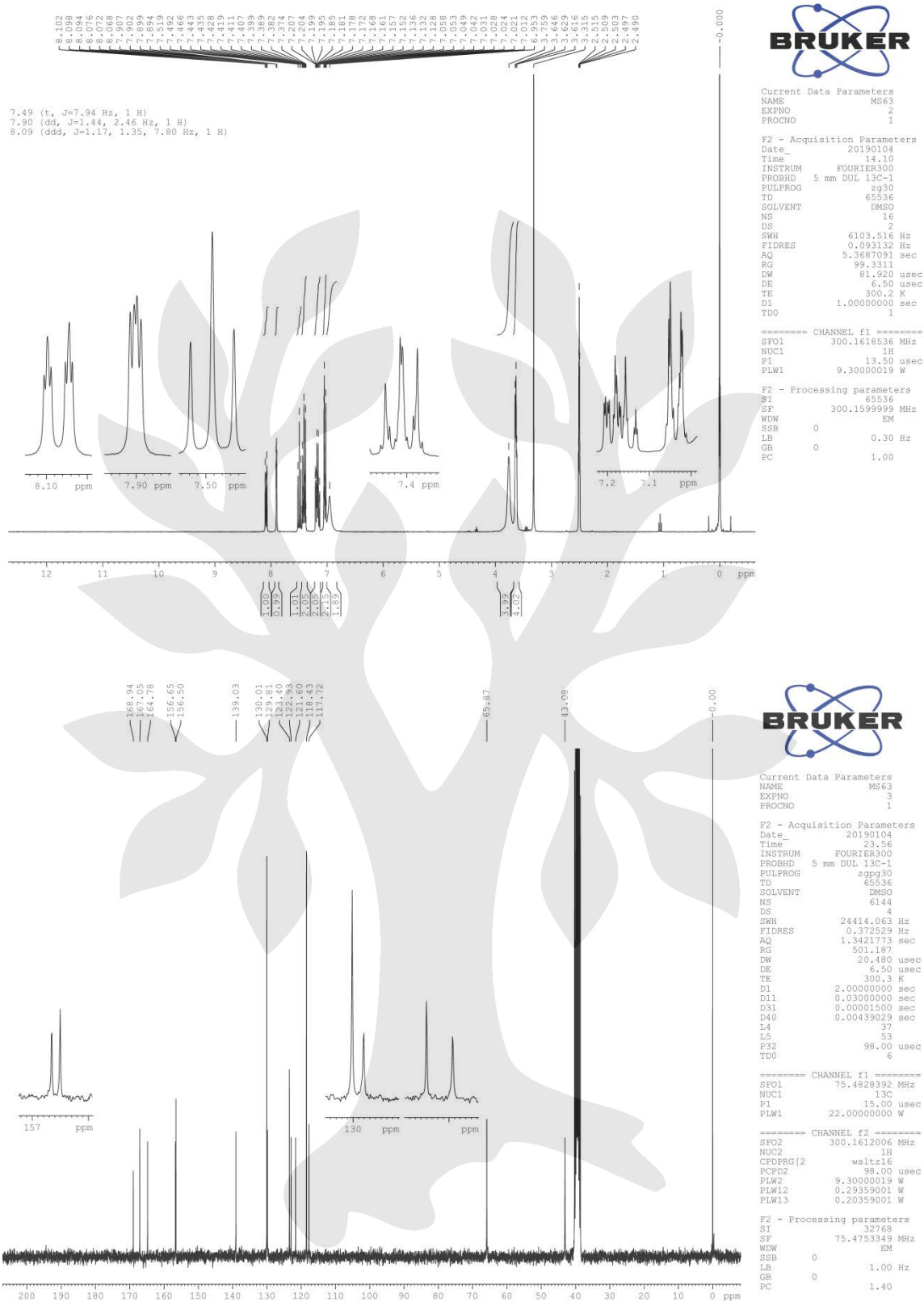
*4-(4-Methoxyphenyl)-6-morpholino-1,3,5-triazin-2-amine (**1i**).*



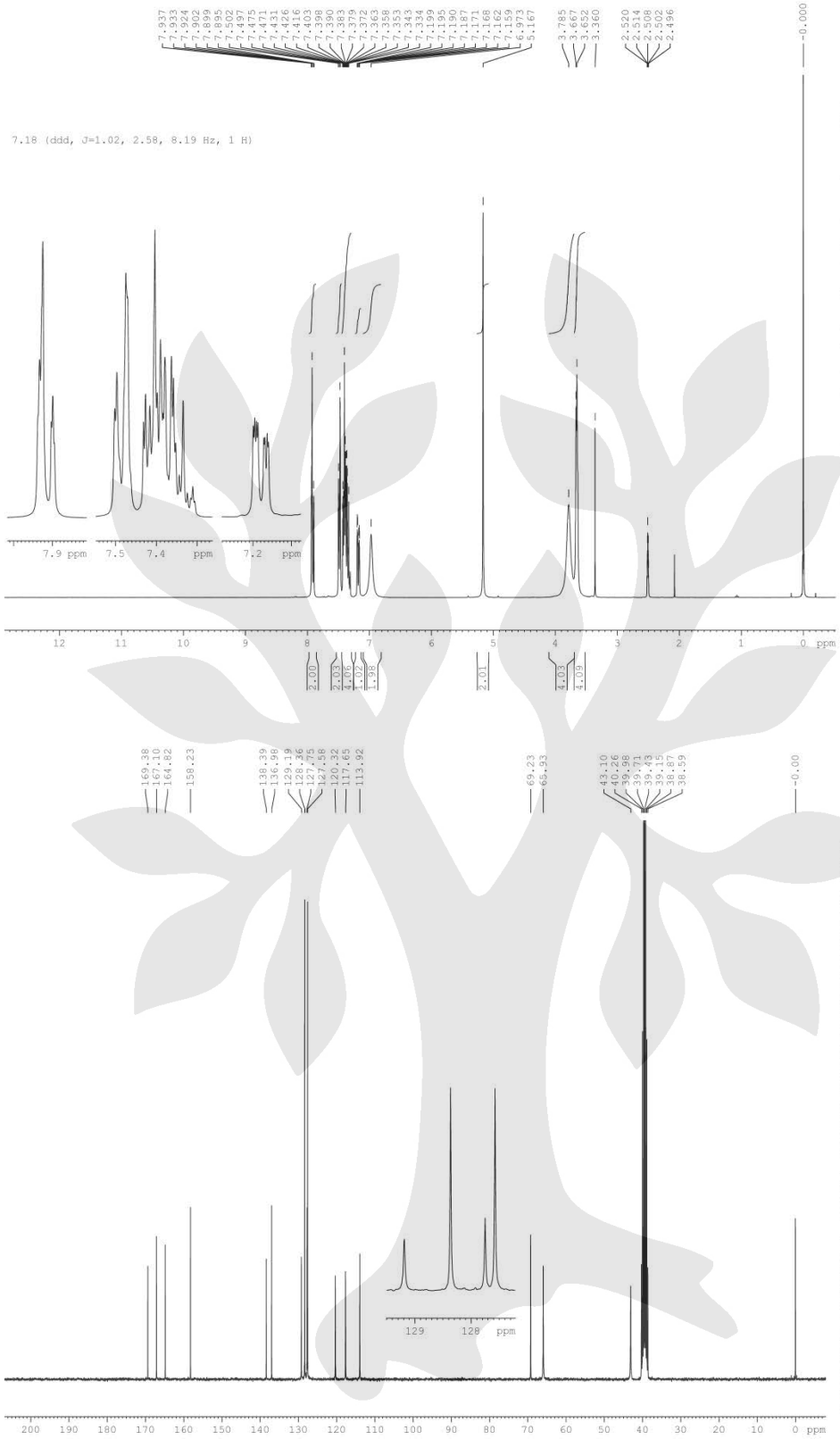
*4-(4-(Trifluoromethoxy)phenyl)-6-morpholino-1,3,5-triazin-2-amine (**1j**).*



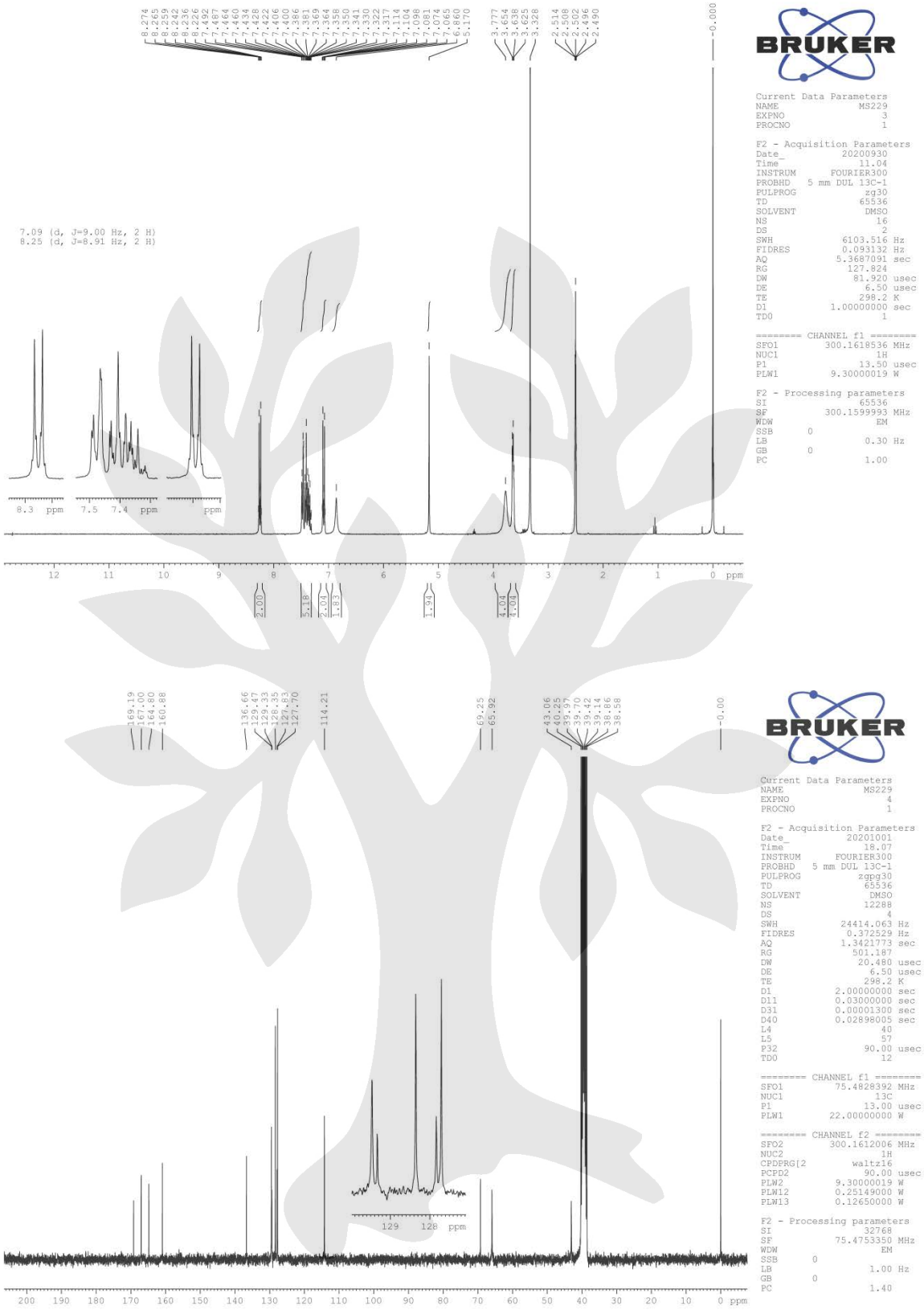
*6-Morpholino-4-(3-phenoxyphenyl)-1,3,5-triazin-2-amine (**1k**).*



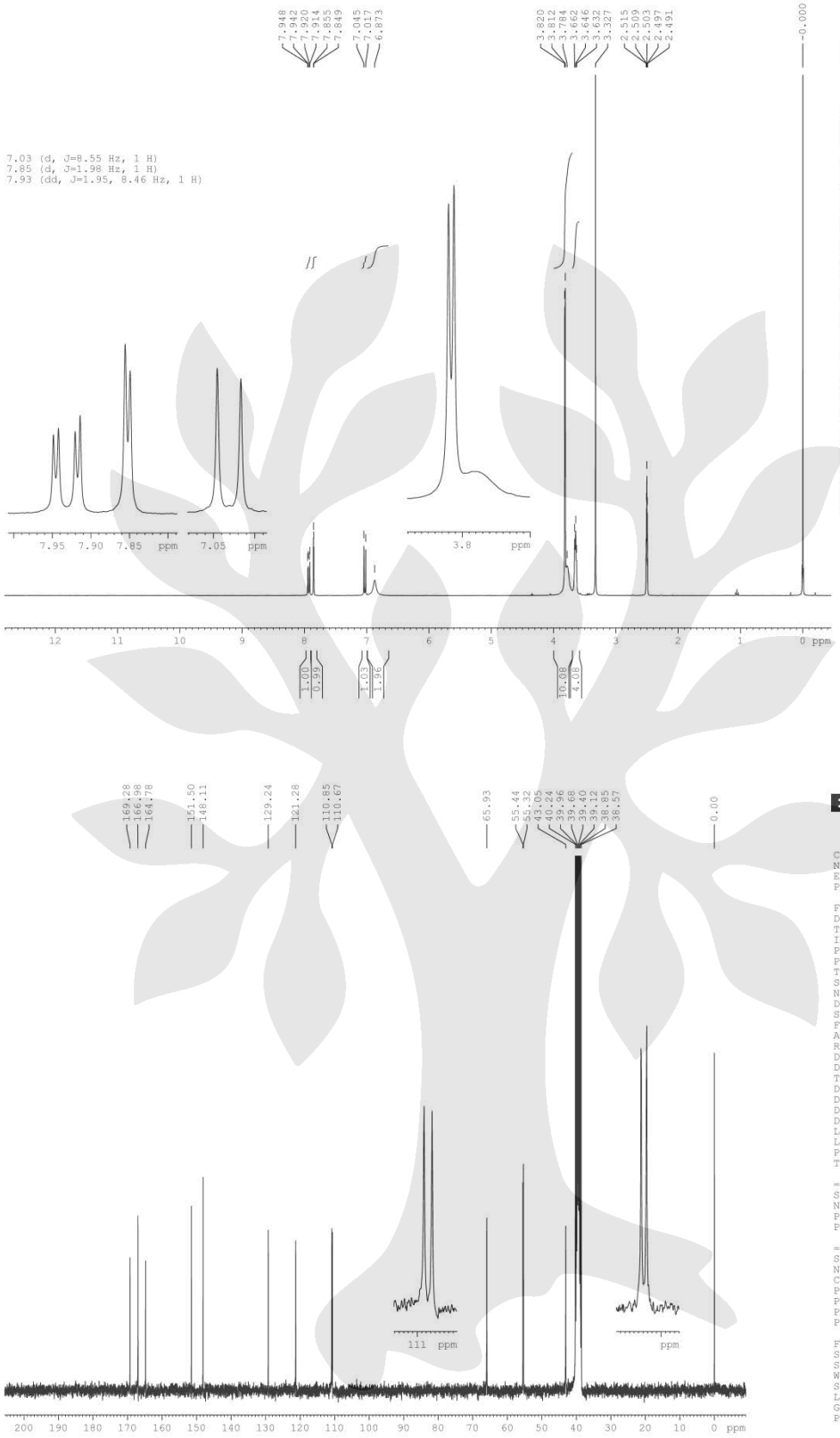
*4-(3-(Benzyloxy)phenyl)-6-morpholino-1,3,5-triazin-2-amine (**1l**).*



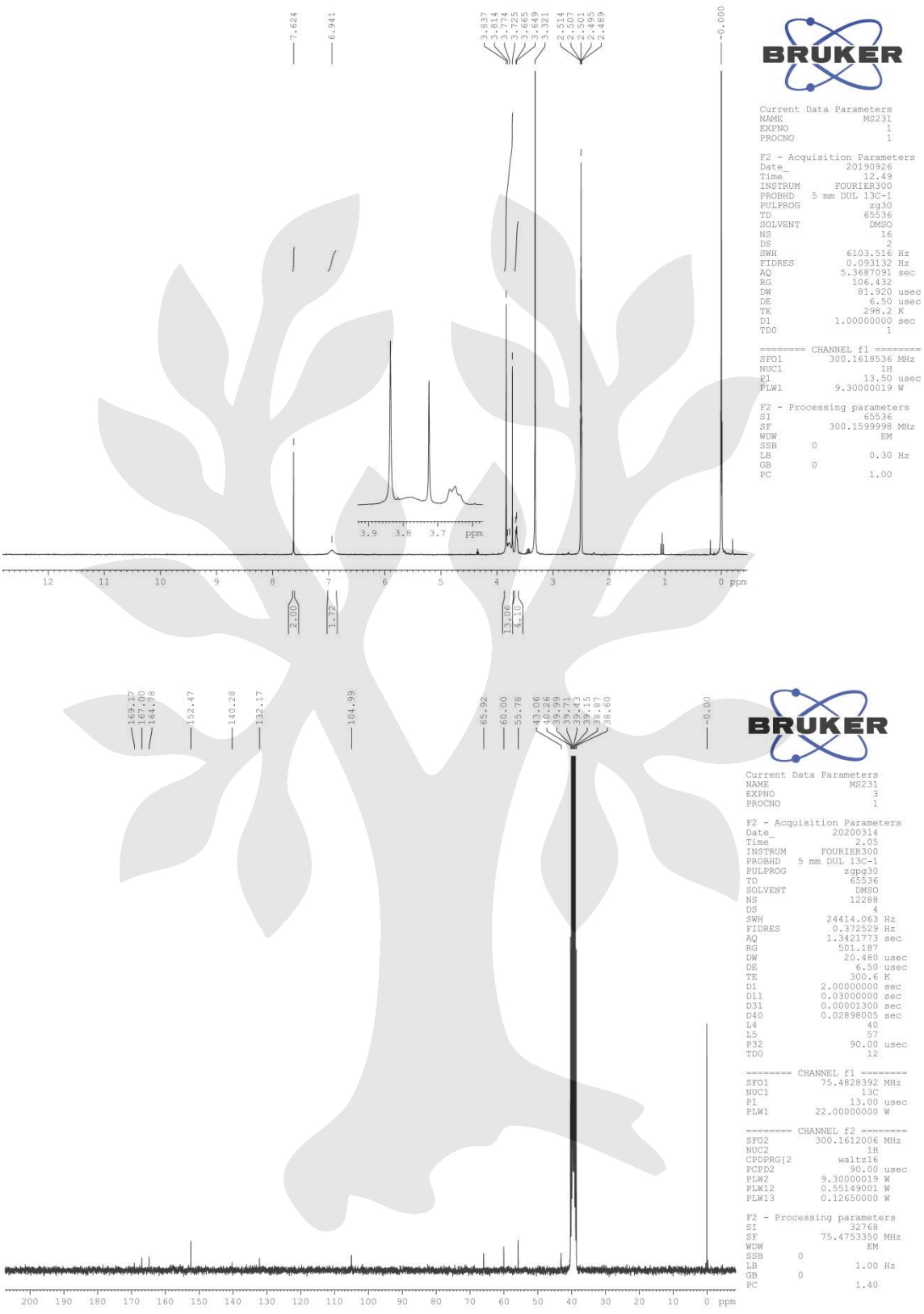
*4-(4-(Benzyloxy)phenyl)-6-morpholino-1,3,5-triazin-2-amine (**1m**).*



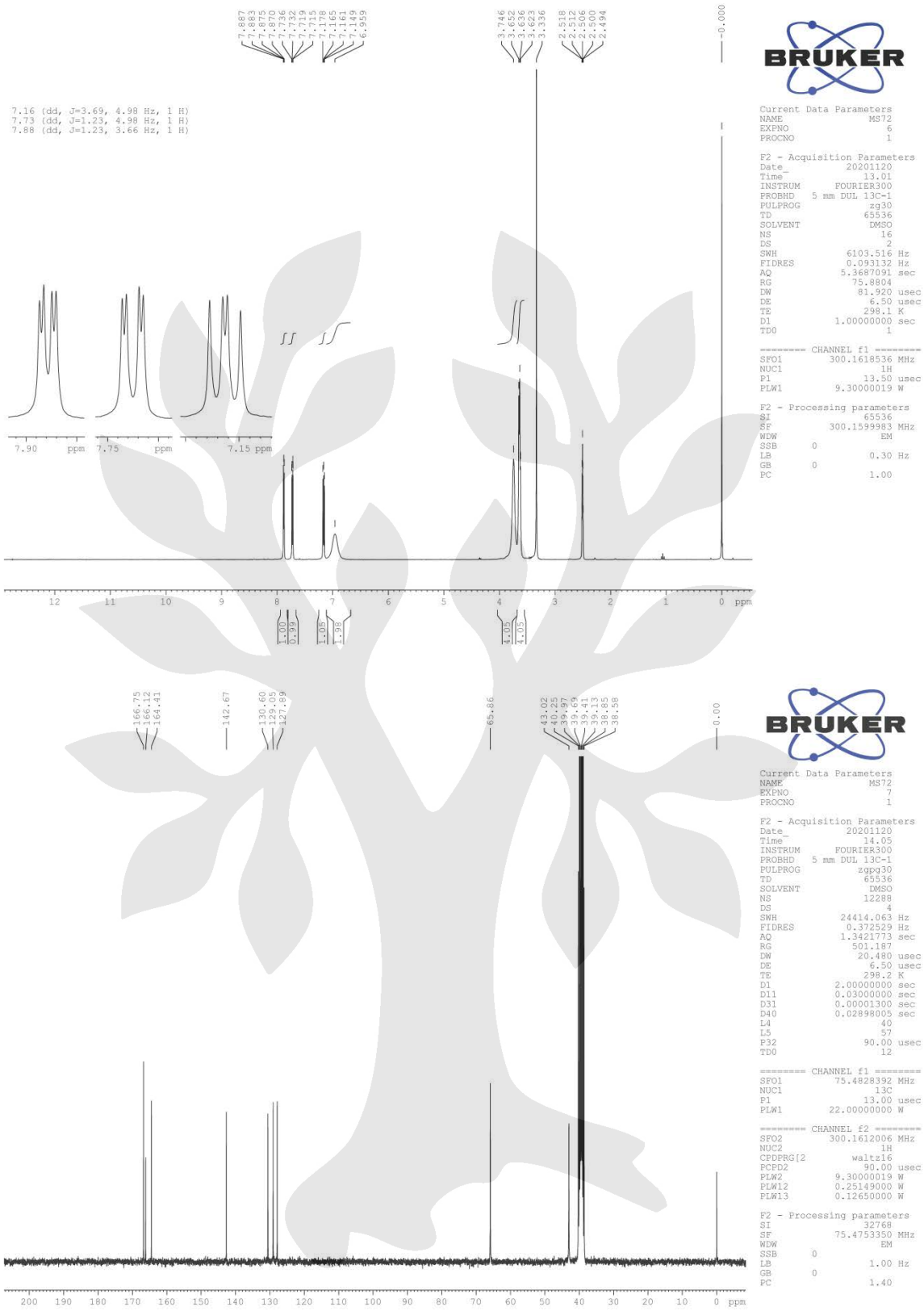
*4-(3,4-Dimethoxyphenyl)-6-morpholino-1,3,5-triazin-2-amine (**1n**).*



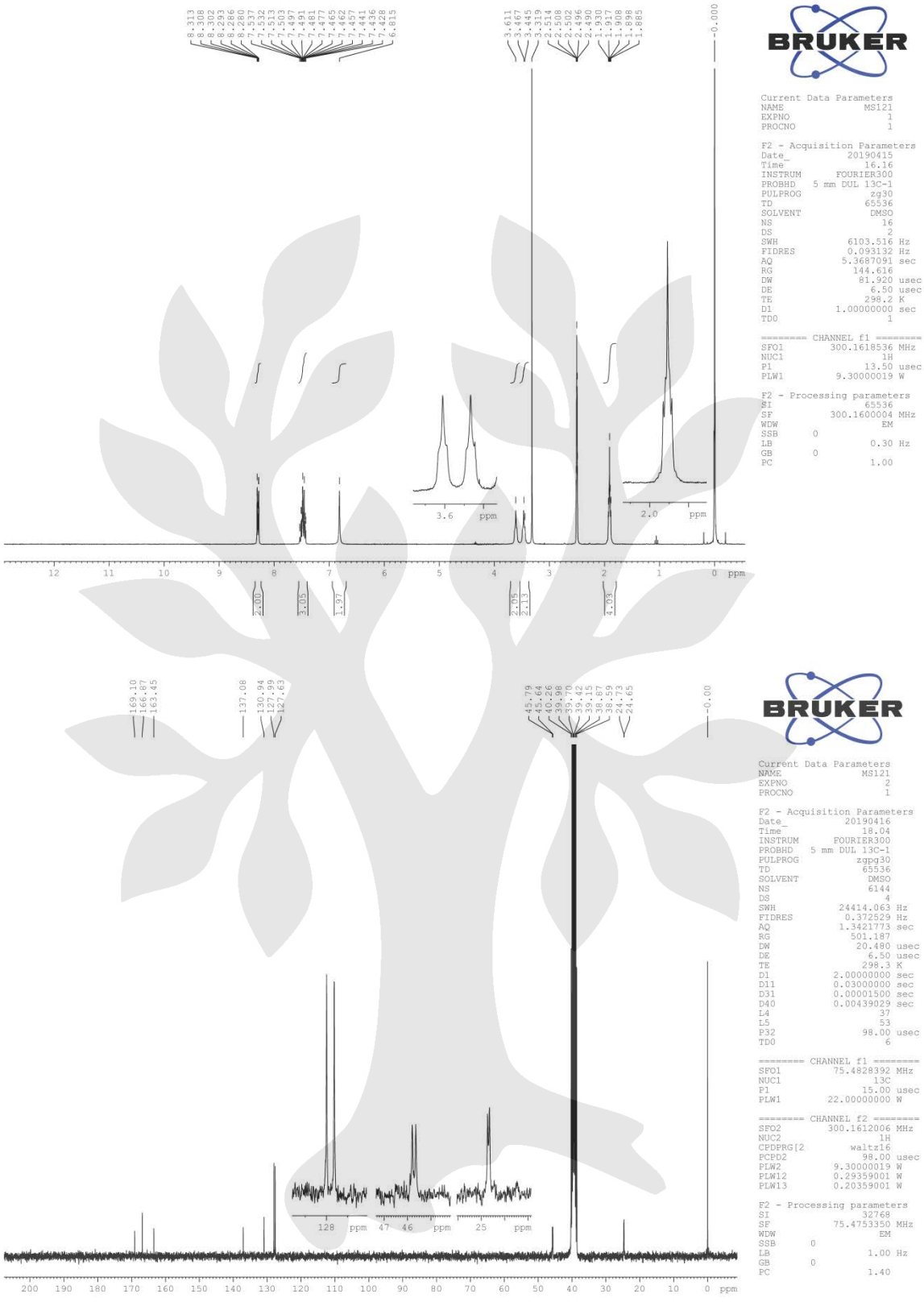
*6-Morpholino-4-(3,4,5-trimethoxyphenyl)-1,3,5-triazin-2-amine (**1o**).*



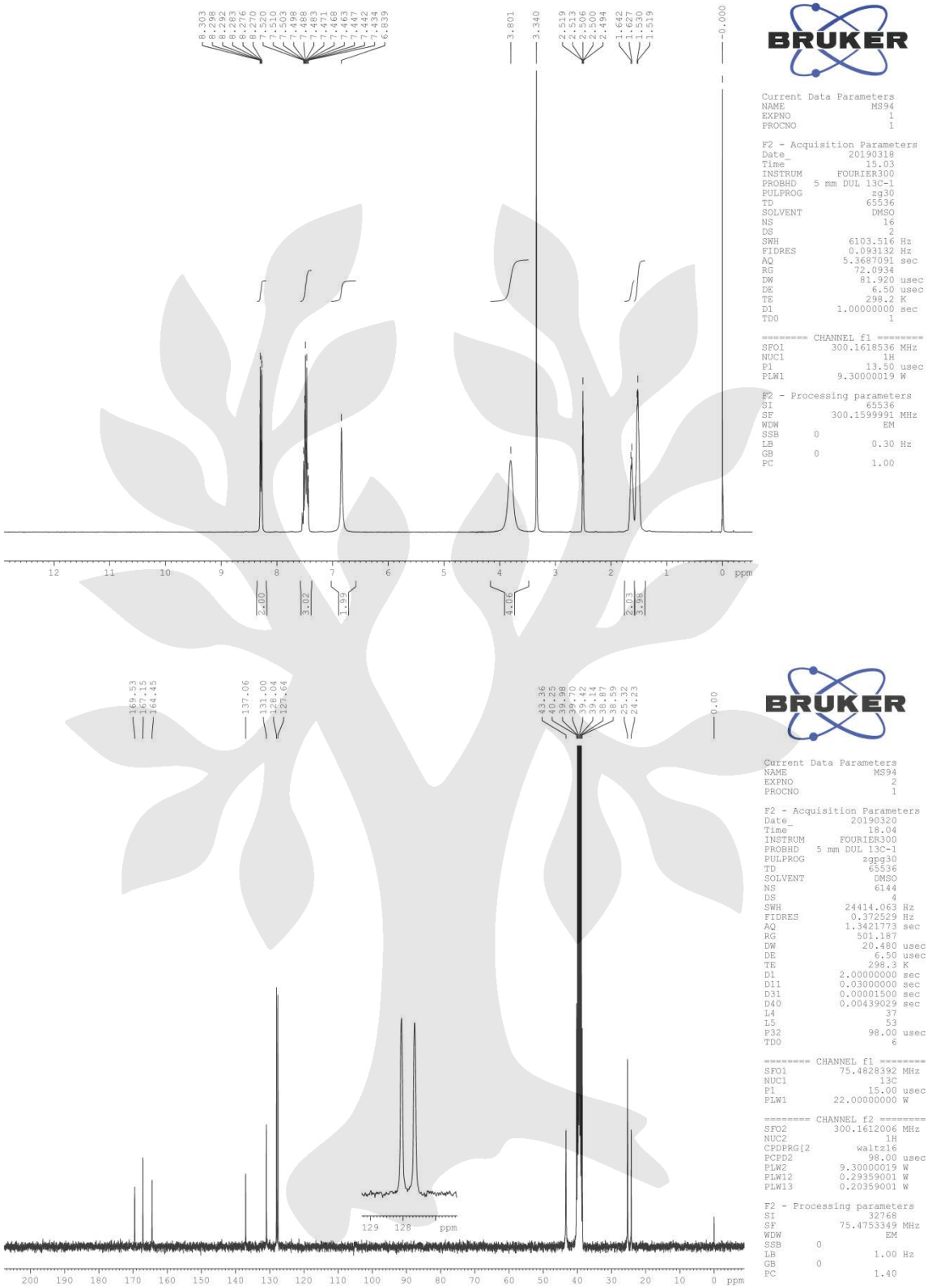
*6-Morpholino-4-(thiophen-2-yl)-1,3,5-triazin-2-amine (**1p**).*



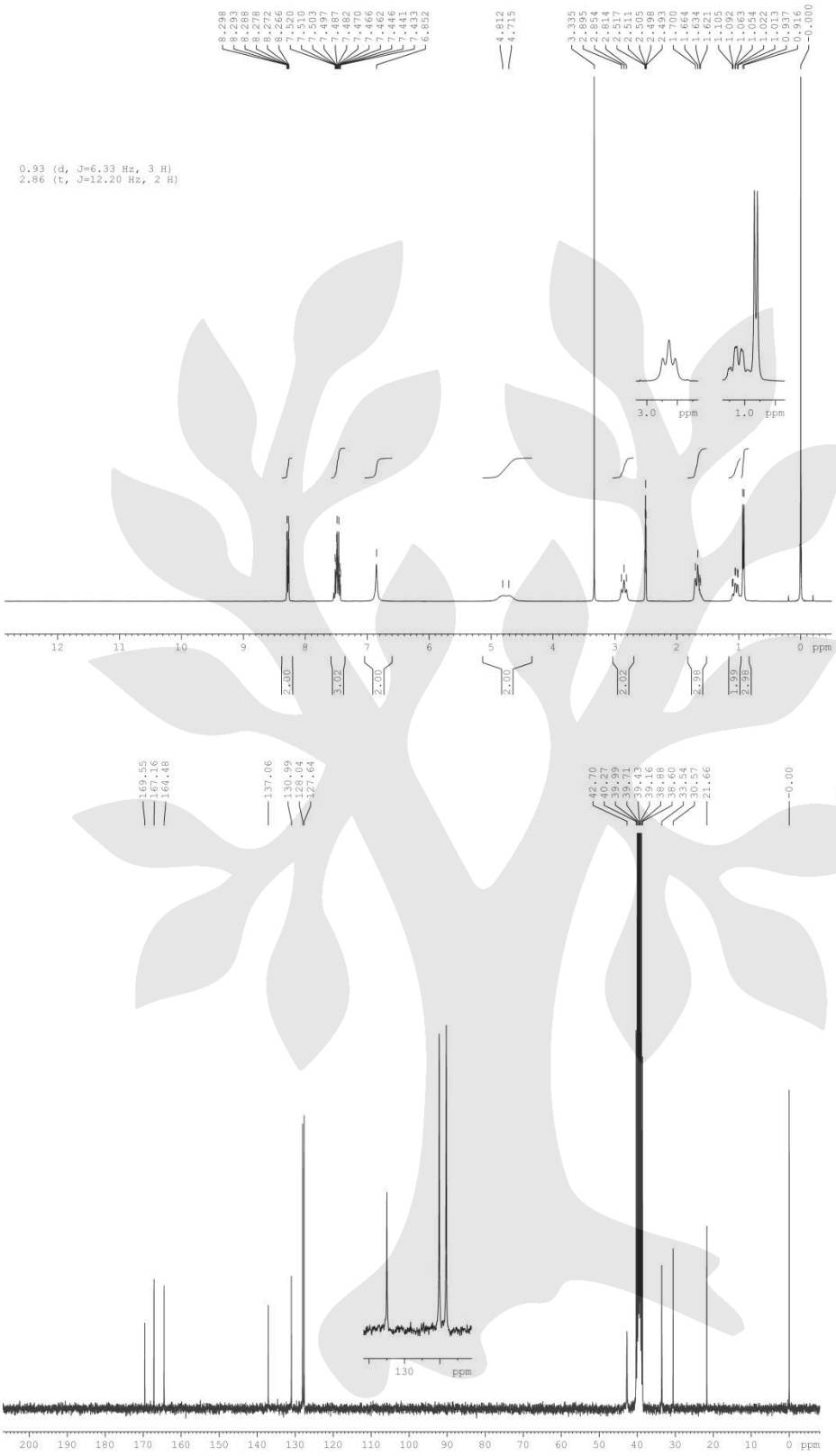
*4-Phenyl-6-pyrrolidino-1,3,5-triazin-2-amine (**1q**).*



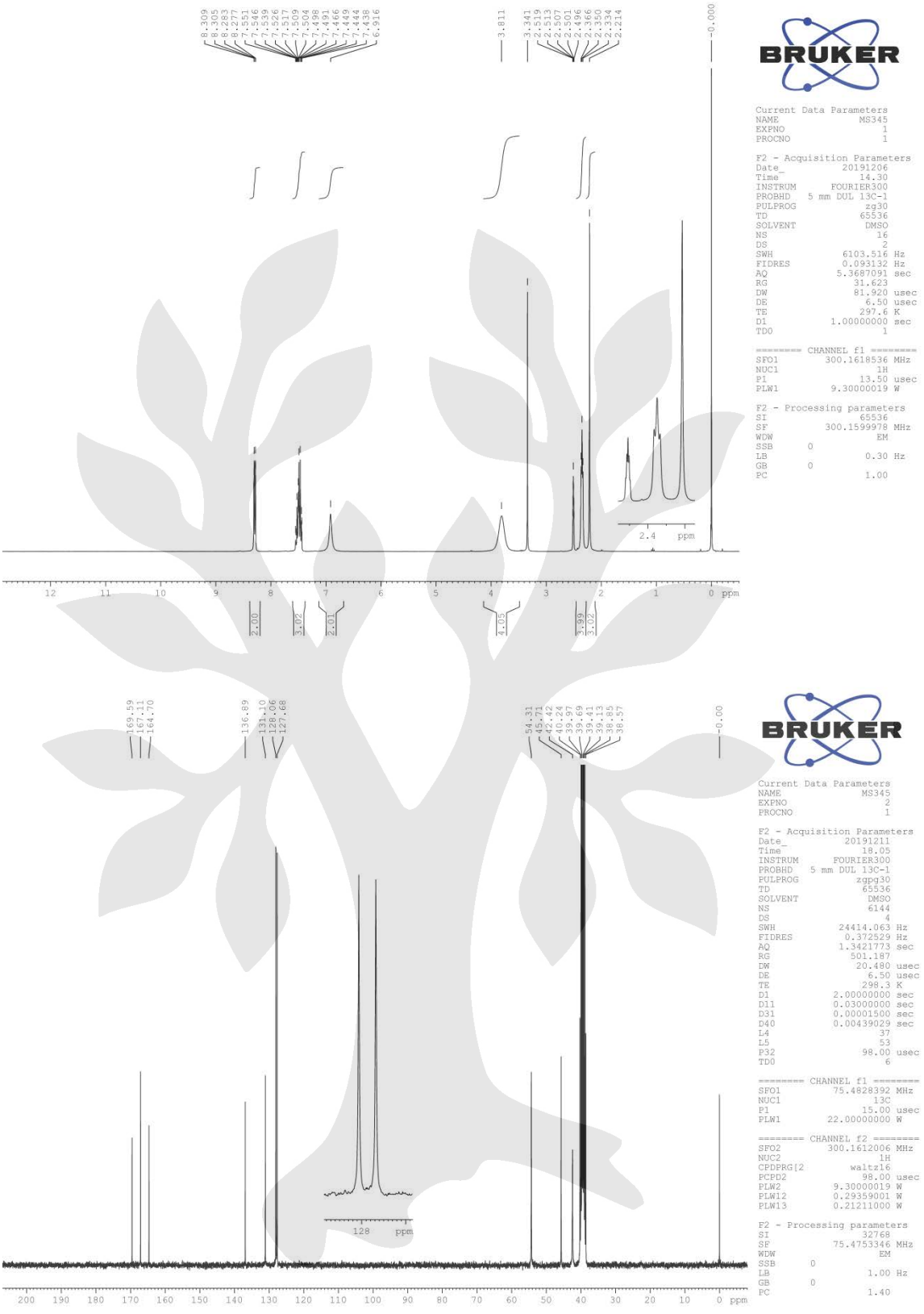
*4-Phenyl-6-piperidino-1,3,5-triazin-2-amine (**1r**).*



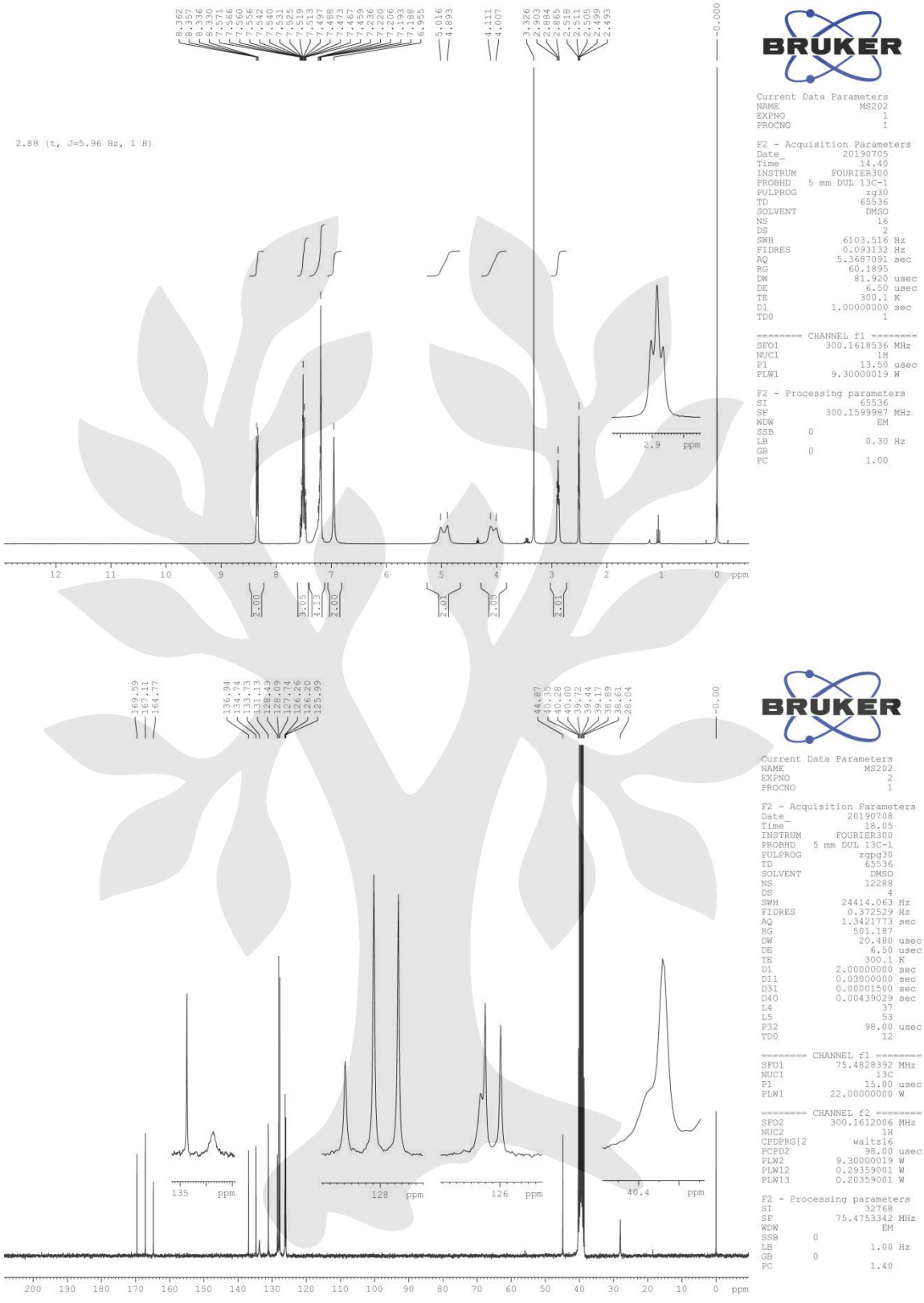
*6-(4-Methylpiperidino)-4-phenyl-1,3,5-triazin-2-amine (**1s**).*



*6-(4-Methylpiperazino)-4-phenyl-1,3,5-triazin-2-amine (**1t**).*



*6-(3,4-Dihydroisoquinolin-2(1H)-yl)-4-phenyl-1,3,5-triazin-2-amine (**1u**).*



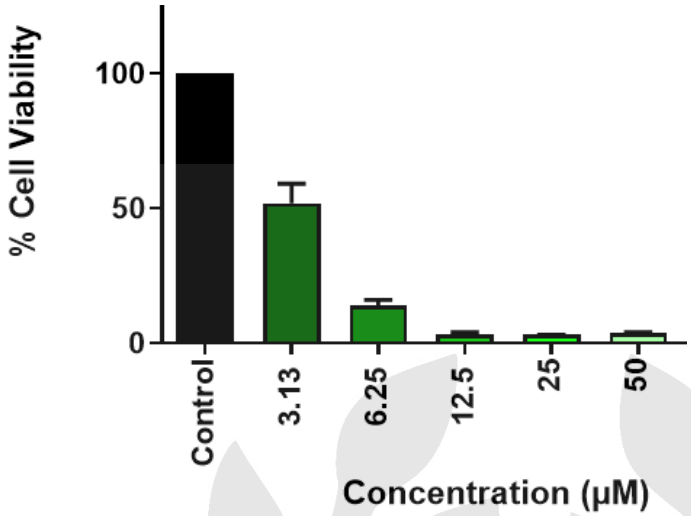


Figure S3. Concentration-dependent antiproliferative effect of **1u** against Jurkat-T cells after the incubation for 72 h.