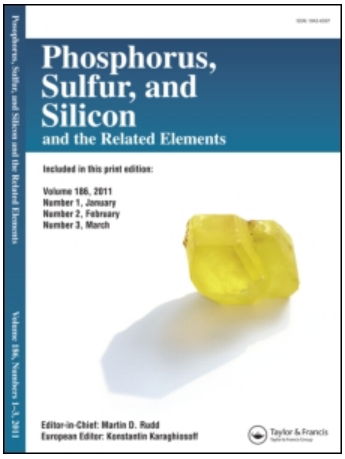

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Eco-Friendly Synthesis and Insecticidal Activity of Some Fluorinated 2-(N-Arylamino)-4-Arylthiazoles

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ECO-FRIENDLY SYNTHESIS AND INSECTICIDAL ACTIVITY OF SOME FLUORINATED 2-(N-ARYLAMINO)-4-ARYLTHIAZOLES

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A series of fluorinated 2-(N-arylamino)-4-arylthiazoles (3) was synthesized by the condensation of appropriate arylthioureas (2) with corresponding α-bromoacetophenones (1) by using "green chemistry" techniques, viz. mechanochemical mixing and microwave or ultrasonic irradiation. Compared with conventional procedures, the reaction can be carried out under milder conditions, requiring a shorter reaction time and giving higher yields following the green chemistry methodology. All the synthesized compounds were characterized on the basis of elemental analyses and spectral data (IR, ^{1}H NMR, and mass spectrometry). Representative compounds were also evaluated for their insecticidal activity against **Helicoverpa armigera*****, and some of them showed promising activity.***

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Keywords Arylthiazoles; arylthioureas; α-bromoacetophenones; eco-friendly synthesis; insecticidal activity; microwave irradiation; sonochemistry

INTRODUCTION

Thiazoles and 2-aminothiazoles are important heterocyclic compounds associated with various pharmacological and biological properties including antimicrobial,[1] anti-inflammatory,[2] antitumor,[3] analgesic,[4] antioxidant,[5] anticonvulsant,[6] antihypertensive,[7] hypoglycemic,[8] and herbicidal[9] activities. Further, incorporation of fluorine into organic compounds enhances their biological activity; in particular the trifluoromethyl substituent has

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shown phytotoxic activity.[10] Ethaboxam,[11] thifluzamide,[12] and metasulfovax[13] are well known commercially available fungicides containing a fluorinated thiazole moiety, widely used in agriculture. Huang and Yang[14] have also reported the microwave-assisted synthesis of polyfluorinated 2-benzylthiobenzothiazoles that showed enhanced fungicidal activity against *R. solani*, *B. cinereapers*, and *D. gregaria.* Pathak and Singh[15] have also reported some fluorinated thiazoles as potent pesticidal agents against *Mesocyclops leuckratti* and observed that substitution of fluorine atom at *para*-position of the aryl moiety enhances the insecticidal activity as compared to substitution by chlorine.

In view of the importance of 2-aminothiazole and its derivatives, various synthetic methods have been developed from time to time, but the Hantzsch reaction of α-halocarbonyl compounds with thioureas is the method of choice.[16] Other methods include the reaction of α-haloketones with KSCN and RNH_2,[17] and ketones with a mixture of NBS, thiourea, and benzoyl peroxide.[18] Solid-supported syntheses have been used to generate small organic libraries,[19] and solution phase chemistry methods utilizing DMF[20] as well as 1,4-dioxane[21] have been reported for combinatorial libraries. Recently, many improved methods have been reported for the synthesis of thiazoles using catalysts such as ammonium 12-molybdophosphate (AMP) in methanol,[22] β-cyclodextrin in water,[23] iodine,[24] and silica chloride,[25] using a solvent such as 1-methyl-2-pyrrolidinone,[26] with the use of microwaves,[27] and using ionic liquids[28] and water.[29] However, in spite of their potential utility, many of these reported methods suffer from drawbacks such as polar and volatile solvents, unsatisfactory yields, cumbersome product isolation procedures, and often expensive catalysts that require a longer reaction time under drastic conditions resulting in generation of aqueous or organic solvent waste.

So the development of a milder, simpler, greener, and more efficient procedure for the synthesis of 2-aminothiazoles is highly desirable. It is currently of prime interest to connect research in chemistry with concerns of environmental protection. So, a number of procedures are now recommended for green chemistry,[30] involving either new eco-friendly reagents and catalysts; selective media such as water, ionic liquids, or solvent-free reactions; or a non-classical mode of activation such as ultrasound or microwaves. Inspired by these observations and in continuation of our research in developing benign and expeditious methods for organic transformations,[31,32] we report in this article the environmentally desirable synthesis of some new 2-(N-arylamino)-4-arylthiazoles (**3**) using solvent-free synthetic methods (microwave irradiation and grinding) and ultrasonication, wherein not only the reaction time has been brought down from hours to minutes in comparison to a conventional heating process, but also results in improved yields. Representative compounds were screened for their insecticidal activity against *Helicoverpa armigera*, showing promising results.

Grindstone chemistry—a greatly evolved version of Toda's method of grinding solids together for solvent free chemical reactions, and also called ball-milling chemistry or mechano-chemistry—is of interest in synthesizing heterocycles because it takes place under mild conditions, in the absence of a solvent, and under eco-friendly conditions.[33] In the grindstone technique, reactions occur through generation of local heat by the grinding of crystals of substrate and reagents by a mortar and pestle, with the transfer of a very small amount of energy. Another solvent-free popular technique is microwave chemistry and can be termed as E-chemistry. Microwave (MW) heating has been used for the rapid synthesis of a variety of compounds, wherein chemical reactions are accelerated because of selective absorption of MW energy by polar molecules, nonpolar molecules being inert

to the MW dielectric loss.[34] The MW irradiation under solvent-free conditions provides unique chemical processes with special attributes such as enhanced reaction rates, higher yields, greater selectivity, and ease of manipulation.[35]

Ultrasound has been used more and more frequently in organic synthesis.[36] Activation of organic reactions with ultrasound constitutes an important and far-reaching domain of modern sonochemistry. This is largely due to the fact that sonochemistry and the recent upsurge of interest in sustainable chemistry share similar aims, such as the use of less hazardous chemicals and environmentally benign solvents while minimizing energy consumption and increasing the selectivity of the product.[37]

To the best of our knowledge, there are no reports in the literature of the preparation of 2-(N-arylamino)-4-arylthiazoles by ultrasonication.

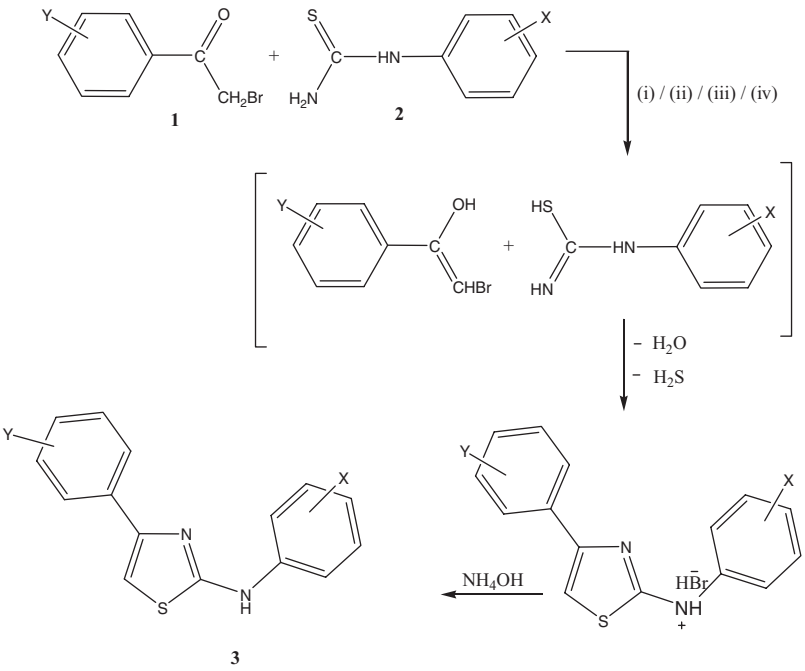
RESULTS AND DISCUSSION

Synthesis

2-(N-Arylamino)-4-arylthiazoles (**3**) were prepared by reacting α-bromoacetophenones (phenacyl bromides) (**1**) and N-aryl substituted thioureas (**2**) by following the classical Hantzsch synthesis using various techniques (Scheme 1). In the traditional approach, the reaction proceeds with low yield (45–58%) after refluxing for 6–8 h in ethanol. In an attempt to improve the yield of reaction and acknowledging the benefits of "green chemistry," the same reaction was performed under solvent-free conditions (microwave irradiation and grinding) and ultrasound irradiation. In the grindstone technique, α-bromoacetophenones and arylthioureas were mixed together by grinding, which was continued for a further 10–15 min to afford the desired compounds in 86–95% yield. The same reactants were thoroughly mixed without solvent and irradiated for 2–5 min in a domestic microwave oven to afford the title compounds in 82–94% yield. Under solvent-free conditions, the reaction is completed within few minutes and with higher yield, due to the reason that a eutectic mixture having uniform distribution of the reactants brings the reacting species in closer proximity to react than in solvent. In the ultrasonic approach, α-bromoacetophenone upon sonication with arylthiourea in an ultrasonic cleaning bath gave 90–97% yield of corresponding thiazole in 1–2.5 h, and the comparative data of various procedures are presented in Table I. The synthetic steps are illustrated in Scheme 1.

In the IR spectra of α-bromoacetophenones (**1a–g**), characteristic >C=O absorption bands appear from 1720–1710 cm^{-1}. The strong absorption band in the range 530–515 cm^{-1} has been attributed to C-Br vibrating modes. In the arylthioureas (**2a–f**), absorption bands at 3421–3380, 3291–3150, and 1580–1540 cm^{-1} are attributed to NH_2, −NH, and >C=S stretching vibrations, respectively. The IR spectra of 2-(N-arylamino)-4-arylthiazoles (**3a–p**) exhibit a broad absorption peak in the region of 3450–3100 cm^{-1} due to >NH stretching vibration. The C=N stretching frequencies have been assigned to the 1560–1530 cm^{-1} region. The bands are mixed with the phenyl ring skeletal vibrations. The prominent peak between 1352–1330 cm^{-1} has been attributed to C=S stretching vibration.

In the ^1H NMR spectra of compounds **1a–g**, $-CH_2$ protons are observed as a singlet at δ 4.40–4.55 ppm. This downfield shift of CH_2 protons is attributed to the e^- withdrawing effect of Br and C=O group. Aromatic protons appear as a multiplet in the region δ 6.97–8.32 ppm. In the compounds **2a–j**, a singlet at δ 10.80–10.91 ppm appears due to a −NH proton. A broad singlet at δ 3.55 ppm is attributed to the $-NH_2$ proton absorption



(i) By ultrasound method
(ii) By microwave method
(iii) By grinding method
(iv) By conventional method

3a: X=H, Y=H
3b: X=H, Y=4-Br
3c: X=H, Y=4-Cl
3d: X=4-Br, Y=4-Br
3e: X=4-Cl, Y=4-Br
3f: X=4-F, Y=4-Br
3g: X=4-Br, Y=4-F
3h: X=3-Cl;4-F, Y=4-Br
3i: X=3-Cl;4-F, Y=4-Cl
3j: X=4-Br, Y=3-CH_3;4-F
3k: X=4-Cl, Y=3-Cl;4-F
3l: X=4-Br,Y=3-Cl;4-F
3m: X=4-Br, Y=2-Cl;4-F
3n: X=4-Cl, Y=2-Cl;4-F
3o: X=3-CF_3, Y=4-Br
3p: X=3-CF_3,Y=4-Cl

Scheme 1 (i) Ultrasound method; (ii) microwave method; (iii) grinding method; (iv) conventional method.

peak. Aromatic proton signals appear as a multiplet from δ 6.68–7.94 ppm. In the ^{1}H NMR spectra of 2-(N-arylamino)-4-arylthiazoles (**3a–p**), the methine proton at C-5 position of thiazole moiety shows a resonance signal at δ 5.95–6.94 ppm, and a N—H resonance signal is observed in the region δ 7.31–7.91 ppm as a singlet, which is D_2O exchangeble. Aromatic protons are observed as a multiplet from δ 6.90–7.80 ppm.

Final confirmation is achieved from fast atomic bombardment (FAB) mass spectra, which exhibit a molecular ion peak (M^+) of compounds **3a–p** corresponding to their molecular masses. Mass spectrum of compound **3h** showed a characteristic molecular ion cluster *m/z* at 382/384 ($[M]^+$, 52.63%) due to the presence of isotopic bromine and a chlorine atom, along with a base peak at 136 ($[M^+$-$C_9H_5BrClF]$, 100%), and other peaks at 308 (18.42), 290 (13.15), 273 (13.15), 168 (10.52), 155 (65.78), 120 (50), 107 (36.84), 88 (23.68), 76 (21.05) were observed.

The presence of fluorine was confirmed by ^{19}F NMR spectra, where the C—F signal was observed at δ −114.84 to −116.78 ppm (compounds **3f–n**) and the CF_3 signal[38] at δ −62.98 to −63.28 ppm in the case of compounds **3o** and **3p**.

Table I Yield (%) and time (min) of the synthesis of 2-(N-arylamino)-4-arylthiazoles (**3a–p**)

	Yield (%)				Time (min)			
Compd. no.	(a)	(b)	(c)	(d)	(a)	(b)	(c)	(d)
3a	90.0	82.0	86.2	45.0	120	3	15	480
3b	91.0	87.7	89.0	47.1	90	3,5	10	450
3c	88.2	85	87.1	46.3	90	3.5	12	435
3d	91.5	90.0	91.0	52.5	90.0	3	10	420
3e	94.8	92.4	93.0	54.7	120	3	12	420
3f	91.0	90.0	90.5	53.8	135	3.5	15	450
3g	92.4	90.0	91.8	56.0	135	4	15	435
3h	97.0	92.1	94.0	58.2	150	3.5	15	480
3i	97.3	92.2	95.5	57.0	150	3.5	15	480
3j	89.0	82.7	84.6	52.0	150	5	20	510
3k	90.0	82.6	88.3	51.0	120	4.5	15	450
3l	96.0	92.3	93.4	58.6	75	4	12	435
3m	96.0	92.0	94.0	57.5	75	4	10	435
3n	95.5	92.8	94.0	56.3	120	4	14	450
3o	97.0	93.8	95.6	58.2	60	2.5	12	360
3p	97.0	94.0	95.0	58.0	60	2	10	360

(a) Ultrasound method; (b) microwave method; (c) grinding method; (d) conventional method.

Insecticidal Activity

In the present study. four thiazoles, **3h**, **3j**, **3o**, and **3p**, were screened for their insecticidal activity, which was measured on third instar larvae of *Helicoverpa armigera* at the Department of Entomology, Agricultural Research Station, Durgapura, Jaipur, India, by food dipping method.[39] Statistical analysis was carried out using completely randomized design (CRD) technique.[40] Please see the Supplemental Materials (available online) for complete details.

EXPERIMENTAL

All the melting points were determined in open glass capillary tubes and are uncorrected. The IR spectra (ν_{max} in cm^{-1}) were recorded on FT IR model Shimadzu-8400S grating infrared spectrophotometer in KBr pellets. ^1H NMR and ^{19}F spectra were measured on JEOL-AL 300 spectrophotometer at 300 MHz, respectively, using TMS as an internal standard (chemical shift in δ ppm) for PMR and CF_3COOH (TFA) as an external standard for ^{19}F NMR and $CDCl_3$ as a solvent. The IR, ^1H NMR, and ^{19}F spectra were recorded at the Department of Chemistry, University of Rajasthan, Jaipur, India. The FAB mass spectra were recorded on JEOL SX 102/DA-6000 mass spectrometer/data system using argon/xenon (6 KV, 10 mA) as the FAB gas. Elentar Vario EL III automatic CHNS analyzer was used for elemental analyses. The FAB mass spectra and CHNS analyses were recorded at Central Drug Research Institute (CDRI), Lucknow, India. Microwave irradiation was carried out in an LG MS-194A household microwave oven with maximum 800 power and 2450 MHz frequency. Sonication was performed in a Toshcon model SW 4 cleaner (with a frequency of 37 KHz and operating at maximum power of 150 W). The purity of the compounds was checked by TLC using silica gel (60–120 mesh) as adsorbent, UV light, or iodine accomplished visualization. All common reagents and solvents were used as

obtained from commercial suppliers without further purification. α–Bromoacetophenones (phenacyl bromides) (**1**) and N-arylthioureas (**2**) were prepared by the methods in the literature.[41–42]

General Procedures for the Preparation of 2-(N-Arylamino)-4-arylthiazoles (3a–p)

Method (i). A mixture of arylthiourea (**2**) (1 mmol) and phenacyl bromide (**1**) (1 mmol) were ground together in a mortar. Then this mixture was transferred into a pyrex conical flask (250 mL). Ethanol (10 mL) was added to it, and then it was sonicated in an ultrasonic cleaning bath for the time period as indicated at room temperature. The reaction flask was immersed in the region of highest intensity from the base of the ultrasonic bath. The bath temperature (30–35°C) was controlled by addition or removal of water. Sonication was continued until the starting reactants disappeared as indicated by TLC. After the completion of the reaction, the mixture was treated with ammonia to liberate the free base, which was then filtered, washed with water, dried, and recrystallized from ethanol to afford the desired product.

Method (ii). Phenacyl bromide (**1**) (1 mmol) and the appropriate arylthiourea (**2**) (1 mmol) were mixed thoroughly using a pestle and mortar. The reaction mixture was then transferred into a conical flask (100 mL) and exposed to microwave irradiation for 2–5 min (intermittently with 1 min cooling interval) at maximum power (800 W). Final temperature of the reaction mixture was measured by immersing a thermometer at the end of the reaction (65–70°C). The progress of the reaction was monitored by TLC using C_6H_6:Pet ether, 80:20 as the solvent system. After cooling to room temperature, the thiazole salt so obtained was neutralized by the addition of a dilute solution of ammonia. The crude product was extracted into methylene chloride (2 × 10 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was recrystallized from ethanol to afford pure 1,3-thiazoles.

Method (iii). A mixture of α-bromoacetophenone (**1**) (1 mmol) and substituted arylthiourea (**2**) (1 mmol) was thoroughly mixed in a mortar followed by grinding until the completion of the reaction as indicated by TLC (10–15 min). Ammonia solution was added to generate the free base of the compound, which was then washed then air dried to afford the crude product. The pure thiazole was obtained by recrystallization from ethanol.

Method (iv). A mixture of the appropriate arylthiourea (**2**) (1 mmol) and phenacyl bromide (**1**) (1 mmol) in ethanol (25 mL) was refluxed for 6–8 h, with occasional shaking on a water bath. After cooling, the precipitated solid was separated and then suspended in water/methanol mixture. Free base was obtained by treating the corresponding hydrobromide salt with ammonia solution until it was alkaline. The precipitated mass was filtered off, washed several times with water, and recrystallized from ethanol.

Preparation of 2-Phenylamino-4-phenylthiazole (3a)

Yield: Method (i) 90%, method (ii) 82%, method (iii) 86.2%, method (iv) 45%; Time (min): (i) 120, (ii) 3, (iii) 15, (iv) 480; mp 136°C; IR (KBr)*v*: 3100 (NH str.), 3018 (aromatic C—H str.), 1531 (C=N str.), 1330 (C=S str), 1600 (aromatic C=C str.) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.31 (s, NH, 1H), 6.90–7.23 (m, ArH, 10H), 5.95 (s, Thiazole H, 1H); FABMS (%) *m/z*: 252 [M^+] (100), 176 (36.01), 160 (15.12), 85 (32.14); Anal. Calcd. (%) for $C_{15}H_{12}N_2S$: C, 71.42; H, 4.76; N, 11.10; S, 12.60. Found: C, 71.27; H, 4.62; N, 11.15; S, 12.52.

Preparation of 2-Phenylamino-4-(4-bromophenyl)thiazole (3b)

Yield: Method (i) 91%, method (ii) 87.7%, method (iii) 89%, method (iv) 47.1%; Time (min): (i) 90, (ii) 3.5, (iii) 10, (iv) 450; mp 195°C; IR (KBr)*v*: 3120 (NH str.), 3020 (aromatic C—H str.), 1535 (C=N str.), 1330 (C=S str.), 1580 (aromatic C=C str.), 560 (C-Br str.) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.42 (s, NH, 1H), 6.95–7.38 (m, ArH, 9H), 5.95 (s, Thiazole H, 1H); FABMS (%) *m/z*: 330[M^+] (100)/332[M+2] (isotopic cluster), 251 (28.12), 175 (15.24), 148 (36.21), 72 (62.09); Anal. Calcd. (%) for $C_{15}H_{11}BrN_2S$: C, 54.54; H, 3.33; N, 8.48; S, 9.69. Found: C, 54.50; H, 3.38; N, 8.42; S, 9.63.

Preparation of 2-Phenylamino-4-(4-chlorophenyl)thiazole (3c)

Yield: Method (i) 88.2%, method (ii) 85%, method (iii) 87.1%, method (iv) 46.3%; Time (min): (i) 90, (ii) 3.5, (iii) 12, (iv) 435; mp 190°C; IR (KBr)*v*: 3150 (NH str.), 3020 (aromatic C—H str.), 1535 (C=N str.), 1330 (C=S str.), 1590 (aromatic C=C str.), 615 (C-Cl str.) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.43 (s, NH, 1H), 6.91–7.20 (m, ArH, 9H), 5.84 (s, Thiazole H, 1H); FABMS (%) *m/z*: 286[M^+] (78.65)/288[M+2] (isotopic cluster), 251 (35.14), 175 (42.63); Anal. Calcd. (%) for $C_{15}H_{11}ClN_2S$: C, 62.93; H, 3.84; N, 9.79; S, 11.18. Found: C, 62.85; H, 3.81; N, 9.71; S, 11.21.

Preparation of 2-(4-Bromophenylamino)-4-(4-bromophenyl)thiazole (3d)

Yield: Method (i) 91.5%, method (ii) 90%, method (iii) 91%, method (iv) 52.5%; Time (min): (i) 90, (ii) 3, (iii) 10, (iv) 420; mp 150°C; IR (KBr)*v*: 3275 (NH str.), 3030 (aromatic C—H str.), 1538 (C=N str.), 1335 (C=S str.), 1595 (aromatic C=C str.), 565 (C-Br) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.65 (s, NH, 1H), 6.94–7.28 (m, ArH, 8H), 6.85 (s, Thiazole H, 1H); FABMS (%) *m/z*: 408[M^+] (100)/410[M+2] (isotopic cluster), 329 (56.23), 250 (34.12), 174 (22.87); Anal. Calcd. (%) for $C_{15}H_{10}Br_2N_2S$: C, 44.11; H, 2.45; N, 6.86; S, 7.84. Found: C, 44.24; H, 2.32; N, 6.82; S, 7.87.

Preparation of 2-(4-Chlorophenylamino)-4-(4-bromophenyl)thiazole (3e)

Yield: Method (i) 94.8%, method (ii) 92.4%, method (iii) 93%, method (iv) 54.7%; Time (min): (i) 120, (ii) 3, (iii) 12, (iv) 420; mp 155°C; IR (KBr)*v*: 3315 (NH str.), 3040 (aromatic C—H str.), 1535 (C=N str.), 1335 (C=S str.), 1594 (aromatic C=C str.), 560 (C-Br), 620 (C-Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.65 (s, NH, 1H), 7.27–7.56 (m, ArH, 8H), 6.83 (s, Thiazole H, 1H); FABMS (%) *m/z*: 364[M^+] (51.43)/366[M+2]/368[M+4] (isotopic cluster), 285 (100), 250 (43.26), 174 (25.68), 133 (18.17); Anal. Calcd. (%) for $C_{15}H_{10}BrClN_2S$: C, 49.45; H, 2.74; N, 7.69; S, 8.79. Found: C, 49.42; H, 2.69; N, 7.64; S, 8.71.

Preparation of 2-(4-Fluorophenylamino)-4-(4-bromophenyl)thiazole (3f)

Yield: Method (i) 91%, method (ii) 90%, method (iii) 90.5%, method (iv) 53.8%; Time (min): (i) 135, (ii) 3.5, (iii) 15, (iv) 450, mp 137°C; IR (KBr)*v*: 3320 (NH str.), 3040 (aromatic C—H str.), 1540 (C=N str.), 1340 (C=S str.), 1595 (aromatic C=C str.), 562 (C-Br), 1141 (C-F) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.85 (s, NH, 1H), 7.24–7.73 (m, ArH, 8H),

6.84 (s, Thiazole H, 1H); ^{19}F NMR ($CDCl_3$) δ: −116.62 (s, F); FABMS (%) *m/z*: 348[M^+] (100)/350[M+2] (isotopic cluster), 269 (71.28), 250 (34.78), 202 (15.17); Anal. Calcd. (%) for $C_{15}H_{10}BrFN_2S$: C, 51.72; H, 2.87; N, 8.04; S, 9.19. Found: C, 51.68; H, 2.72; N, 8.07; S, 9.09.

Preparation of 2-(4-Bromophenylamino)-4-(4-fluorophenyl)thiazole (3g)

Yield: Method (i) 92.4%, method (ii) 90%, method (iii) 91.8%, method (iv) 56%; Time (min): (i) 135, (ii) 4, (iii) 15, (iv) 435, mp 131°C; IR (KBr)*v*: 3320 (NH str.), 3040 (aromatic C−H str.), 1540 (C=N str.), 1340 (C=S str.), 1595 (aromatic C=C str.), 570 (C-Br), 1130 (C-F) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.62 (s, NH, 1H), 7.10–7.54 (m, ArH, 8H), 6.75 (s, Thiazole H, 1H); ^{19}F NMR ($CDCl_3$) δ: −115.92 (s, F); FABMS (%) *m/z*: 348[M^+] (65.34)/350[M+2] (isotopic cluster), 329 (54.27), 299 (100), 144 (17.14); Anal. Calcd. (%) for $C_{15}H_{10}BrFN_2S$: C, 51.72; H, 2.87; N, 8.04; S, 9.19. Found: C, 51.69; H, 2.93; N, 8.09; S, 9.10.

Preparation of 2-(3-Chloro-4-fluorophenylamino)-4-(4-bromophenyl) thiazole (3h)

Yield: Method (i) 97%, method (ii) 92.1%, method (iii) 94%, method (iv) 58.2%; Time (min): (i) 150, (ii) 3.5, (iii) 15, (iv) 480, mp 180°C; IR (KBr)*v*: 3370 (NH str.), 3050 (aromatic C−H str.), 1542 (C=N str.), 1345 (C=S str.), 1600 (aromatic C=C str.), 560 (C-Br), 625 (C-Cl), 1150 (C-F) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.82 (s, NH, 1H), 7.01–7.60 (m, ArH, 7H), 6.84 (s, Thiazole H, 1H);^{19}F NMR ($CDCl_3$) δ: −114.99 (s, F); FABMS (%) *m/z*: 382[M^+] (52.63)/384[M+2]/386[M+4] (isotopic cluster), 308 (18.42), 290 (13.15), 273 (13.15), 168 (10.52), 155 (65.78), 136 (100) 120 (50); Anal. Calcd. (%) for $C_{15}H_9BrClFN_2S$: C, 47.12; H, 2.35; N, 7.32; S, 8.37. Found: C, 47.08; H, 2.29; N, 7.26; S, 8.34.

Preparation of 2-(3-Chloro-4-fluorophenylamino)-4-(4-chlorophenyl) thiazole (3i)

Yield: method (i) 97.3%, method (ii) 92.2%, method (iii) 95.5%, method (iv) 57%; Time (min): (i) 150, (ii) 3.5, (iii) 15, (iv) 480; mp 110°C; IR (KBr)*v*: 3380 (NH str.), 3050 (aromatic C−H str.), 1545 (C=N str.), 1345 (C=S str.), 1610 (aromatic C=C str.), 650 (C-Br), 1150 (C-F) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.83 (s, NH, 1H), 7.05–7.61 (m, ArH, 7H), 6.86 (s, Thiazole H, 1H);^{19}F NMR ($CDCl_3$) δ: −114.84 (s, F); FABMS (%) m/z: 338[M^+] (56.23)/340[M+2] (isotopic cluster), 303 (47.38), 268 (31.25), 249 (18.23), 155 (100); Anal. Calcd. (%) for $C_{15}H_9Cl_2FN_2S$: C, 53.25; H, 2.66;N,8.28, S,9.46. Found: C, 53.16; H, 2.60; N, 8.21; S, 9.43.

Preparation of 2-(4-Bromophenylamino)-4-(4-fluoro-3-methylphenyl) thiazole (3j)

Yield: Method (i) 89%, method (ii) 82.7%, method (iii) 84.6%, method (iv) 52%; Time (min): (i) 150, (ii) 5, (iii) 20, (iv) 510; mp 170°C; IR (KBr)*v*: 3310 (NH str.), 3030 (aromatic C−H str.), 2990 (aliphatic C-H str.), 1535 (C=N str.), 1340 (C=S str.), 1590 (aromatic C=C str.), 560 (C-Br) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.56 (s, NH, 1H), 7.10–7.47

(m, ArH, 7H), 5.95 (s, Thiazole H, 1H); 1.25 (s, CH_3, 3H); ^{19}F NMR ($CDCl_3$) δ: −115.33 (s, F); FABMS (%) m/z: 362[M^+] (100)/364[M+2] (isotopic cluster), 347(42.65), 328 (18.64), 249 (15.09), 173 (64.28); Anal. Calcd. (%) for $C_{16}H_{12}BrFN_2S$: C, 53.03; H, 3.31; N, 7.73; S, 8.83. Found: C, 53.08; H, 3.25; N, 7.65; S, 8.80.

Preparation of 2-(4-Chlorophenylamino)-4-(3-chloro-4-fluorophenyl) thiazole (3k)

Yield: Method (i) 90%, method (ii) 82.6%, method (iii) 88.3%, method (iv) 51%; Time (min): (i) 120, (ii) 4.5, (iii) 15, (iv) 450; mp 168°C; IR (KBr)*v*: 3380 (NH str.), 3052 (aromatic C−H str.), 1546 (C=N str.), 1348 (C=S str.), 1610 (aromatic C=C str.), 615 (C-Cl) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.74 (s, NH, 1H), 7.18–7.70 (m, ArH, 7H), 6.82 (s, Thiazole H, 1H); ^{19}F NMR ($CDCl_3$) δ: −115.18 (s, F); FABMS (%) m/z: 338[M^+] (46.14)/340[M+2] (isotopic cluster), 319 (52.15), 284 (37.33), 249 (41.24), 208 (100); Anal. Calcd. (%) for $C_{15}H_9Cl_2FN_2S$: C, 53.25; H, 2.66; N, 8.28; S, 9.46. Found: C, 53.29; H, 2.62; N, 8.21; S, 9.44.

Preparation of 2-(4-Bromophenylamino)-4-(3-chloro-4-fluorophenyl) thiazole (3l)

Yield: Method (i) 96%, method (ii) 92.3%, method (iii) 93.4%, method (iv) 58.6%; Time (min): (i) 75, (ii) 4, (iii) 12, (iv) 435; mp 177°C; IR (KBr)*v*: 3370 (NH str.), 3050 (aromatic C−H str.), 1543 (C=N str.), 1346 (C=S str.), 1600 (aromatic C=C str.), 565 (C-Br) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.63 (s, NH, 1H), 7.01–7.65 (m, ArH, 7H), 6.76 (s, Thiazole H, 1H); ^{19}F NMR ($CDCl_3$) δ: −114. 95 (s, F); FABMS (%) *m/z*: 382[M^+] (54.52)/384[M+2]/386[M+4] (isotopic cluster), 363 (41.29), 328 (78.14), 249 (64.59), 173 (15.85), 132 (100); Anal. Calcd. (%) for $C_{15}H_9BrClFN_2S$ C, 47.12; H, 2.35; N, 7.32; S, 8.37. Found: C, 47.01; H, 2.30; N, 7.29; S, 8.33.

Preparation of 2-(4-Bromophenylamino)-4-(2-chloro-4-fluorophenyl) thiazole (3m)

Yield: Method (i) 96%, method (ii) 92%, method (iii) 94%, method (iv) 57.5%; Time (min): (i) 75, (ii) 4, (iii) 10, (iv) 435; mp 174°C; IR (KBr)*v*: 3410 (NH str.), 3048 (aromatic C−H str.), 1540 (C=N str.), 1345 (C=S str.), 1600 (aromatic C=C str.), 560 (C-Br), 620 (C-Cl) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.64 (s, NH, 1H), 7.02–7.66 (m, ArH, 7H), 6.75 (s, Thiazole H, 1H);^{19}F NMR ($CDCl_3$) δ: −116.67 (s, F); FABMS (%) *m/z*: 382[M^+] (100)/384[M+2]/386[M+4] (isotopic cluster), 303 (81.28), 268 (75.79), 249 (45.03), 208 (31.93); Anal. Calcd. (%) for $C_{15}H_9BrClFN_2S$: C, 47.12; H, 2.35; N, 7.32; S, 8.37. Found: C, 47.05; H, 2.28; N, 7.21; S, 8.32.

Preparation of 2-(4-Chlorophenylamino)-4-(2-chloro-4-fluorophenyl) thiazole (3n)

Yield: Method (i) 95.5%, method (ii) 92.8%, method (iii) 94%, method (iv) 56.3%; Time (min): (i) 120, (ii) 4, (iii) 14, (iv) 450; mp 165°C; IR (KBr)*v*: 3410 (NH str.), 3045 (aromatic C−H str.), 1540 (C=N str.), 1345 (C=S str.), 1610 (aromatic C=C str.), 650

(C-Cl), 1160 (C-F) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.82 (s, NH, 1H), 7.16–7.76 (m, ArH, 7H), 6.80 (s, Thiazole H, 1H);^{19}F NMR ($CDCl_3$) δ: −116.78 (s, F); FABMS (%) *m/z*: 338[M^+] (65.14)/340[M+2] (isotopic cluster), 319 (25.09), 284 (100), 249 (50.25); Anal. Calcd. (%) for $C_{15}H_9Cl_2FN_2S$: C, 53.25; H, 2.66; N, 8.28; S, 9.46. Found: C, 53.18; H, 2.70; N, 8.22; S, 9.43.

Preparation of 2-(3-Trifluoromethylphenylamino)-4-(4-bromophenyl) thiazole (3o)

Yield: Method (i) 97%, method (ii) 93.8%, method (iii) 95.6%, method (iv) 58.2%; Time (min): (i) 60, (ii) 2.5, (iii) 12, (iv) 360; mp 140°C; IR (KBr)*v*: 3450 (NH str.), 3055 (aromatic C−H str.), 1555 (C=N str.), 1350 (C=S str.), 1615 (aromatic C=C str.), 570 (C-Cl), 1190 (C-F) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.91 (s, NH, 1H), 7.27–7.69 (m, ArH, 8H), 6.90 (s, Thiazole H, 1H);^{19}F NMR ($CDCl_3$) δ: −63.28 (s, CF_3); FABMS (%) *m/z*: 398[M^+] (100)/400[M+2] (isotopic cluster), 329 (48.17), 250 (54.08), 234 (21.15); Anal. Calcd. (%) for $C_{16}H_{10}BrF_3N_2S$: C, 48.24; H, 2.51; N, 7.03; S, 8.04. Found: C, 48.20; H, 2.57; N, 7.09; S, 8.08.

Preparation of 2-(3-Trifluoromethylphenylamino)-4-(4-chlorophenyl) thiazole (3p)

Yield: Method (i) 97%, method (ii) 94%, method (iii) 95%, method (iv) 58%; Time (min): (i) 60, (ii) 2, (iii) 10, (iv) 360; mp 85°C; IR (KBr)*v*: 3452 (NH str.), 3060 (aromatic C−H str.), 1560 (C=N str.), 1352 (C=S str.), 1620 (aromatic C=C str.), 560 (C-Br), 625 (C-Cl);1195 (C-F) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.91 (s, NH, 1H), 7.25–7.80 (m, ArH, 8H), 6.94 (s, Thiazole H, 1H);^{19}F NMR ($CDCl_3$) δ: −62.98 (s, CF_3); FABMS (%) m/z: 354[M^+] (100)/356[M+2] (isotopic cluster), 285 (25.85), 250 (41.57), 174 (56.04), 158 (63.21); Anal. Calcd. (%) for $C_{16}H_{10}ClF_3N_2S$: C, 54.23; H, 2.82; N, 7.90; S, 9.03. Found: C, 54.18; H, 2.74; N, 7.86; S, 9.09.

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