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SYNTHESIS OF SOME NOVEL THIAZOLE, THIOPHENE, THIENOPYRIDINE AND THIENOPYRIMIDINE DERIVATIVES CONTAINING TOSYL MOIETY

S. HESSIEN
Chemistry Department, Faculty of Science (girls), Al -Azhar University, Cairo, Egypt.

MONA KADAH
Chemistry Department, Faculty of Science (girls), Al -Azhar University, Cairo, Egypt.

N. MARZOUK
Chemistry Department, Faculty of Science (girls), Al -Azhar University, Cairo, Egypt.

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SYNTHESIS OF SOME NOVEL THIAZOLE, THIOPHENE, THIENOPYRIDINE AND THIENOPYRIMIDINE DERIVATIVES CONTAINING TOSYL MOIETY

S. A. HESSIEN, MONA S. KADAH AND N. A. MARZOUK

Al-Azhar University, Faculty of Science (Girls), Chemistry Department, Cairo, Egypt.

Abstract

Interaction of 4-aminoacetophenone (1) with p-tolyl sulphonamide afforded 1-[4-tosyl amino) phenyl]ethanone (2).

Treatment of 2 with bromine water yielded 2-bromo-1-[4-tosyl amino) phenyl]ethanone (3), which reacted with thiourea to give 2-amino thiazole derivative (4). Compound 2 was condensed with phenyl acetaldehyde and malononitrile to give derivatives (5) and (7), which were respectively reacted with o-aminothiophenol and carbon disulfide to give derivatives (6) and (9). Reaction of 7 under Gewald reaction condition afforded the thiophen-3-carbonitrile derivative (11) which consequently reacted with 4-fluorobenzylidinemalononitrile, phenyl isothiocyanate to give compounds 12 and 15, respectively. The structures of these compounds were confirmed by infrared, mass and ^{1}H-NMR spectra. The measurement of potential cytotoxicity for the compound 11 was tested and has exhibit anticancer of liver and breast.

Introduction

Activated nitriles have attracted considerable interest as potential building blocks for many nitrogen containing heterocyclic system[1-3]. Also, derivatives of thiazole, pyridine and pyrimidine show a variety of pharmacological effects[4-6]. Furthermore tosyl derivatives show marked biological activity[7].

Thus, the aim of the present work is the synthesis of thiazoles, thiophene, thienopyridine and thienopyrimidine containing tosyl moiety to investigate their potential activity.

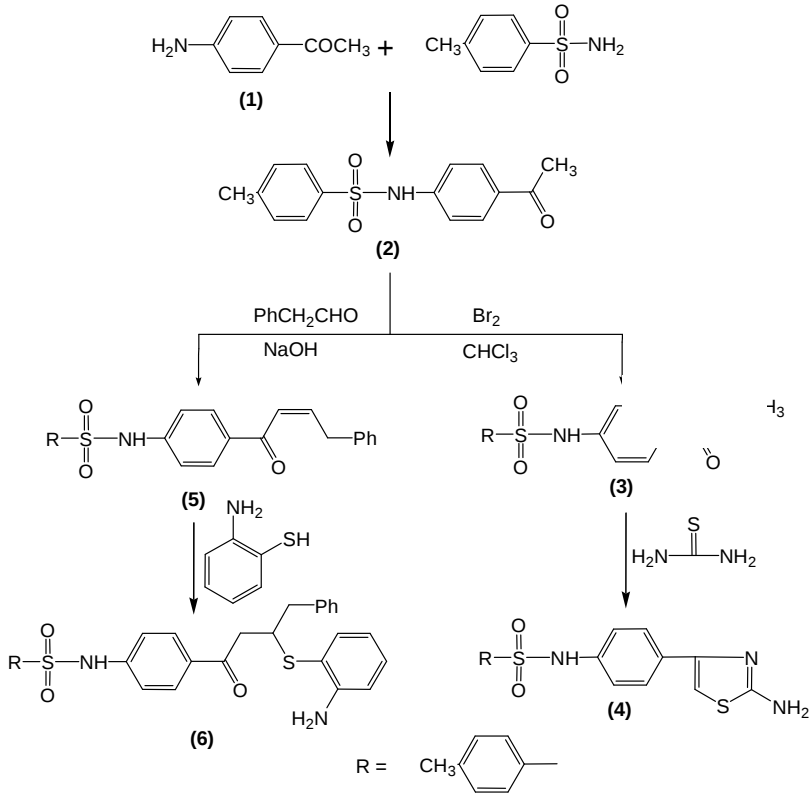
Results and Discussion

The various prepared compounds are outlined in Schemes 1-3. Reaction of 4-aminoacetophenone (1) with p-tolyl sulphonamide afforded 1-[4-tosyl amino) phenyl]ethanone (2). Structure of compound 2 was established by correct analytical data.

Treatment of 2 with bromine water in chloroform provided 2-bromoethanone derivative (3), which reacted with thiourea to afford 2-amino thiazole derivative (4) which is in accordance with previous work[8].

In addition, compound 2 reacted with phenyl acetaldehyde in ethanolic sodium hydroxide solution to give phenyl but-2-en-1-one derivative (5), which reacted with o-aminothiophenol to give phenyl butan-1-one derivative (6) which is in accordance with previous work[9].

The assigned structure of compounds (3), (4), (5) and (6) was supported by analytical and spectral data.



(Scheme 1)

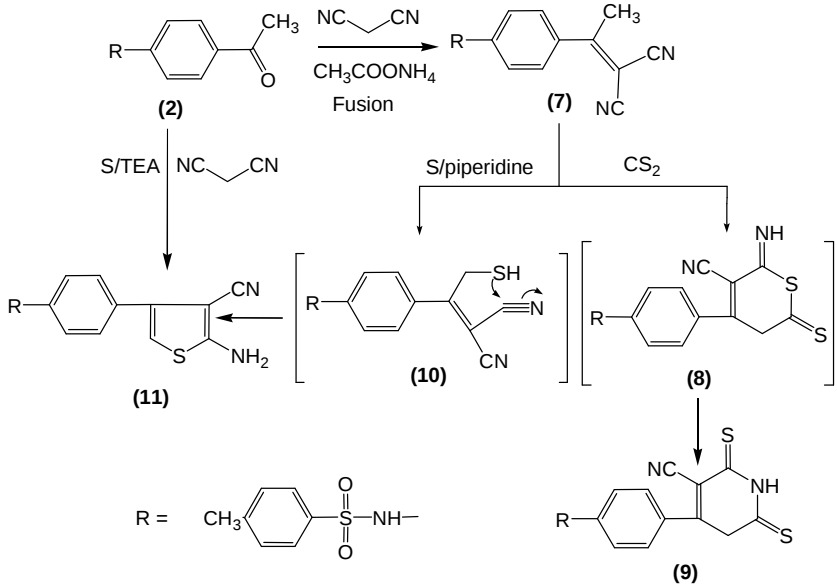
As an extension for the synthesis of the target compound the enamino nitrile, the authors focused on incorporating compound 2 with different reagent in the hope of obtaining compounds with different applications. Thus compound 2 was fused with malononitrile in the presence of ammonium acetate to give ethylidinemalononitrile derivative (7).

The reactivity of methyl function in compound 7 towards carbon disulfide and sulfur were investigated. Thus interaction of 7 with carbon disulfide yield thiazine derivative (8) which rearranged into pyridin-2,6-dithione derivative (9), which is in accordance with previous work[1,10].

The assigned structure of compound (7), and compound (9) were supported by spectroscopic and elemental data.

Treatment of 7 with elemental sulfur under Gewald reaction conditions[11] furnished 2-amino thiophen-3-carbonitrile derivative (11). The formation of compound 11 occurred via thiation of methyl group in compound 7 to give 10 as an intermediate followed by intramolecular cyclization. Compound 11 was in agreement with analytical and spectral data.

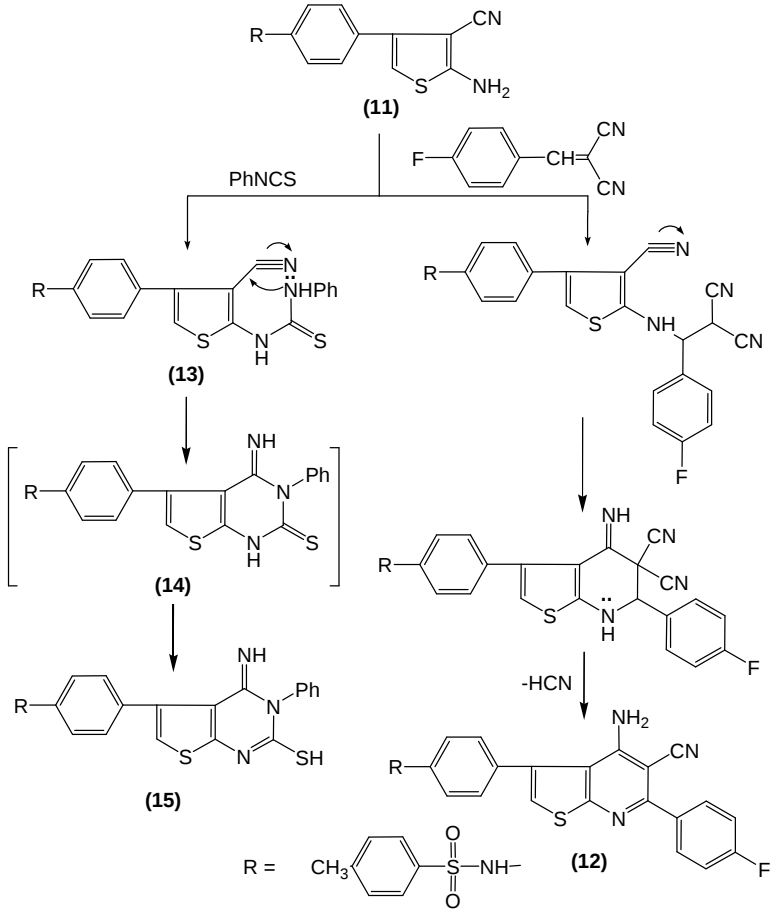
Compound 11 was also obtained directly by interaction of ketone 2 with a mixture of malononitrile and elemental sulfur in presence of few drops of triethyl amine.



Scheme (2)

Compound 11 was proved to be a versatile starting material for the synthesis of some novel thienopyridine and thienopyrimidine derivatives. Thus, the interaction of 11 with 4-fluorobenzylidene malononitrile gives thienopyridine derivative (12). The reaction was proceed via Michael type addition of NH_2 followed by cyclization and HCN elimination. Compound 12 was supported by correct analytical data and spectral data.

Furthermore, the interaction of 11 with phenylisothiocyanate led to the formation of thiourea derivatives (13), which cyclized after stirring with sodium ethoxide to a product that may be formulated as 14 which rearranged to the more stable isomeric derivative 15, which is in accordance with previous work[12].



Scheme (3)

Experimental

All melting points were uncorrected. The IR-spectra were recorded on Pyeunicam sp/1100 spectrophotometer. ^{1}HNMR spectra were recorded in $CDCl_3$ or in DMSO-d_6 on a varian 90, 200 MHz spectrometer. Mass spectra were performed by a Shimadzu GC-

MSQP 100 Ex (Shimadzu, Japan). Elemental analysis were carried out by the Microanalytical Research Center, Faculty of Science, Cairo University. Pharmacology was carried in National Tumor Institute, Cairo University.

Synthesis of 1-[4-(tosyl amino)phenyl]ethanone (2)

To a solution of 1 (0.01 mol) and p-tolylsulphonamide (0.01 mol) in ethanol 50 ml was added few drops of piperidine. The reaction mixture was stirred for about 30 min. Then the solvent was removed and the solid obtained was crystallized from ethanol to give 2 (Table 1). Structure of compound 2 was established by correct analytical data and infrared spectrum which revealed absorption bands at 3220 cm^{-1} for NH and 1670 cm^{-1} (C=O) group.

while, its ^{1}H-NMR of 2 (DMSO-d_6) showed signals at δ 1.83 (s, 3H, CH_3), δ 2.51 (s, 3H, $COCH_3$), δ 7.2-7.8 (d-d, 8H, Ar-H) and δ 10.8 (s, 1H, NH).

Synthesis of 2-bromo-1-[4-(tosyl amino)phenyl]ethanone (3)

To a solution of 2 (0.01 mol) in chloroform (200 ml) was added bromine (0.5 ml) in chloroform (25 ml) while shaking for half an hour. The reaction mixture was heated for fifteen minutes on a water bath to expel most of the hydrogen bromide, cooled and filtered. The solid separated was washed with ether giving pure product, which crystallized from ethanol to give 3, (Table 1).

Structure 3 was established by correct analytical and spectral data where IR showed 835 cm^{-1} (Br), 1665 (C=O) and 3319 (NH). Its mass spectrum afforded a molecular ion peak m/z 369 [M^{+}, 57%] with a base peak at 120 [$PhCOCH_3$] and the following abundant peaks at m/z 77 (30.6%), 92 (59.2%), 234 (40.8%) and 330 (76.2%).

Synthesis of 4-[4-(tosyl amino)phenyl]thiazol-2-amine (4)

To a suspension of 3 (0.008 mol) in hot ethanol (15 ml) was treated with thiourea (0.02 mol) a smooth exothermic reaction took place giving a clear solution that soon deposits crystals. The deposit crystals were filtered, washed with ethanol and recrystallized from benzene. The structure of 4 was established by analytical and spectroscopic evidence, (Table 1).

The IR spectrum of 4 showed the disappearance of carbonyl group found in parent compound and showed the absorption bands at 1620 (C=N), 3100 and 3194 & 3328 cm^{-1} [NH/NH_2], ^{1}HNMR spectrum in (DMSO-d_6) showed signals at δ 2.2 (s, 3H, CH_3), δ 6.24 (s, 2H, NH_2), 6.94 (s, 1H, thiazole), 7.1-7.52 (dd, 4H, Ar), 7.2-7.8 (m, 4H, Ar-H) and 9.0 (s, 1H, NH).

Synthesis of 4-phenyl-1-[4-(tosyl amino)phenyl]but-2-en-1-one (5)

To a mixture of 2 (0.01 mol) and phenyl acetaldehyde (0.01 mol) in ethanol (30 ml), 10% alcoholic sodium hydroxide (5 ml) was added. The reaction mixture was stirred at room temperature for 3 hr. The reaction mixture was acidified with hydrochloric acid and the resulting solid was filtered, washed with water and recrystallized from ethanol to give 5. The structure of 5 was confirmed from elemental analysis and mass spectrum which exhibited a molecular ion peak at m/z 391 [M^+, 37.5%], with base peak at 77 (100%) and other abundant peaks at m/z 296 (37.5%) and 231 (18.8%).

Synthesis of 3-(2-aminophenylthio)-4-phenyl-1-[4-(tosyl amino)-phenyl]butan-1-one (6)

A mixture of o-aminothiophenol (0.01 mol), compound 5 (0.01 mol) and piperidine (0.2 ml) in benzene (50 ml) was refluxed for 2 hr. The solid obtained after cooling was recrystallized from ethanol to give 6, (Table 1).

IR spectrum of 6 showed a characteristic broad band at 3227 cm^{-1}, 3194 cm^{-1}& 3102 cm^{-1} (NH/NH_2) and 1655 (C=O).

Mass spectrum of 6 showed a molecular ion peak M^+ at m/z 361 (9.05%) and the base peak observed at 91. In addition, other peaks at 106 (14.01%), 155 (29.1%) and 225 (2%) were observed.

^{1}H-NMR in (DMSO-d_6) revealed signals at δ 2.32 (s, 3H, CH_3), δ 3.37 (s, 2H, NH_2), δ 5.47-5.95 (m, 5H, $2CH_2$ + CH), δ 7.18-7.38 (m, 9H, Ar), δ 7.70-7.85 (d-d, 8H, Ar-H), δ 10.83 (s, 1H, NH).

Synthesis of 2-[1-methyl-1-(4-tosyl amino)phenyl]ethylidene) malononitrile (7)

A mixture of 1 (0.01 mol), malononitrile (0.01 mol) and ammonium acetate (0.2 g) was fused for 6 hr. The solid obtained was washed with petroleum ether (40-60oC) and crystallized from ethanol to give 7 (Table 1).

Infrared spectrum of 7 showed absorption bands at 3279 cm^{-1} (NH) and broad bands at 2198 for 2(C≡N) groups. ^{1}H-NMR in (DMSO-d_6) showed signals at δ 2.10 (s, 3H, CH_3), δ 3.10 (s, 3H, CH_3), δ 7.10-7.84 (d-d, 8H, Ar-H) and δ 10.80 (s, 1H, NH).

Synthesis of 3-cyano-4-[4-(tosyl amino)phenyl]pyridin-2,6(1H,5H)-dithione (9)

To a solution of 7 (0.01 mol) in pyridine (5 ml), carbon disulfide (0.01 mol) was added and the solution was refluxed for 8 h in water bath. After cooling, methanol (30 ml) was added and the solid separated was filtered and washed with P.E. 80-100°C, then crystallized from methanol to give 9, (Table 1).

Infrared spectrum of 9 showed absorption bands at 3331, 3218 cm^{-1} (2NH), 2220 cm^{-1} (C≡N) group, 1601 cm^{-1} (C=S). ^{1}H-NMR in (DMSO-d_6) showed signals at δ 1.89 (s, 3H, CH_3), δ 4.21 (s, 2H, CH_2), δ 7.20-8.10 (m, 8H, Ar-H), δ 10.35 and 10.85 (2s, 2H, 2NH).

Synthesis of 2-amino-4-[4-(tosyl amino)phenyl]thiophen-3-carbonitrile (11)

Method A:

A solution of 7 (0.01 mol) and sulfur powder (0.01 mol) in ethanol (50 ml) containing few drops of piperidine, was refluxed for 3h. The reaction mixture was cooled, the solid obtained was crystallized from ethanol to give 11. IR spectrum of 11 showed absorption bands at 3408, 3320, 3208 cm^{-1} (NH_2/NH), 2206 cm^{-1} (C≡N). ^{1}H-NMR in (DMSO-d_6) which afforded signals at δ 1.75 (s, 3H, CH_3), δ 5.07 (s, 2H, NH_2), δ 7.10 (s, 1H, thiophene) and δ 7.13-7.63 (m, 9H, Ar-H + NH).

Method B:

A mixture of 2 (0.01 mol), malononitrile (0.01 mol) and sulfur powder (0.01 mol) was refluxed in ethanol (50 ml) containing few drops of triethylamine for 2h. The solid obtained after filtrate was recrystallized from ethanol to give one and the same compound 11, (Table 1).

Synthesis of 4-amino-2-(4-fluorophenyl)-5-[4-(tosyl amino)phenyl] thieno[2,3-b]pyridin-3-carbonitrile (12)

Equimolar amounts of 11 (0.01 mol) and 4-flourobenzylidene malononitrile (0.01 mol) was refluxed in ethanol (30 ml) in presence of drops of piperidine for 3h. The solid obtained after concentration and cooling was crystallized from ethanol to give 12. Compound 12 was supported by correct analytical data and ^{1}HNMR (DMSO-d_6) afforded signals at δ 1.62 (s, 3H, CH_3), δ 3.71 (s, 2H, NH_2), δ 6.21 (s, 1H, thiophene-H), δ 7.02-7.48 (m, 9H, Ar-H + NH) and 7.70-7.82 (d-d, 4H, Ar-H).

Synthesis of N-phenyl-N`-4-[4-(tosyl amino)phenyl]thiophen-2-yl]thiourea (13)

A solution of 11 (0.01 mol) and phenylisothiocyanate (0.01 mol) in dry benzene (20 ml) containing triethylamine (0.2 ml) was refluxed for 20h. The solvent was distilled off and the obtained product was filtered and recrystallized from ethanol to give 13. The IR spectrum of 13 showed absorption bands at 3320, 3238 and 3218 cm^{-1} (3NH) and 2221 cm^{-1} (C≡N) group. Mass spectrum of 13 exhibited a molecular ion peak m/z 504 [14%] with a base peak at 51 and other abundant peaks at 186 (35%) and 131 (28%), (Table 1).

Synthesis of 3-N-phenyl-4-imino-5-[4-(tosyl amino)phenyl]thieno [2,3-d]pyrimidin-2-thiol (15)

Compound 13 (0.01 mol) and sodium ethoxide (0.01 mol in 30 ml ethanol) was stirred at room temperature for 3 hr. The reaction

mixture was cooled and the resulting product was filtered and crystallized from ethanol to give 15, (Table 1).

The assigned structure of 15, was confirmed by correct analytical data and IR spectrum which revealed the disappearance of cyano group found in the parent compound and showed characteristic band at 3135 cm^{-1} (NH) and at 1610 cm^{-1} (C=N).

Pharmacology

Measurement of potential cytotoxicity by SRB assay:

Potential cytotoxicity of compound (11) was tested using the method of Skehan[13].

- Cells were plated in 96-multiwell plate (10^4 cells/well) for 24 hr before treatment with the compound (11) to allow attachment of cell to the wall of the plate.
- Different concentration of the compound under test (0, 1, 2.5, 5 and 10 μg/ml) were added to the cell monolayer triplicate wells were prepared for each individual dose.
- Monolayer cells were incubated with the compound (11) for 24 hr at 37ºC and in atmosphere of 5% CO_2.
- After 48 hr, cells were fixed, washed and stained with Sulfo-Rhodamine-B stain.
- Excess stain was washed with acetic acid and attached stain was recovered with Tris EDTA buffer.
- Color intensity was measured in an ELISA reader.
- The relation between surviving fraction and drug cone, is plotted to get the survival curve of each tumor cell line after the specified compound.

Report about the cytotoxicity activity

2-Aminothiophene-3-carbonitrile derivative (11) was tested for any cytotoxicity activity using tumor cell lines.

1- U251 (brain tumor cell line)

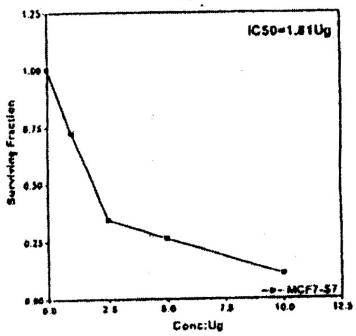
2- HEPG2 (liver carcinoma cell line)
3- MCF7 (breast carcinoma cell line)
4- H460 (lung carcinoma cell line)
5- HELA (cervix carcinoma cell line)
6- HCT116 (colon carcinoma cell line)
7- HEP2 (larynx carcinoma cell line)

At compound concentration between (1-10 jig) using the SRB assay.

Drug cytotoxicity

Conc:Ug	MCF7-S7
0.0	1.00000
1.0	0.72512
2.5	0.34461
5.0	0.26162
10.0	0.11442

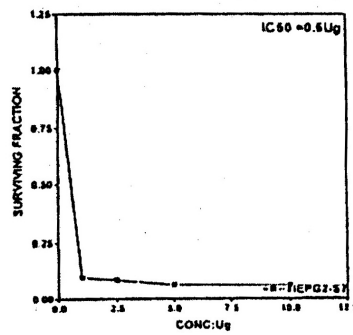
MCF7



DRUG CYTOTOXICITY

CONC:Ug	HEPG2-S7
0.0	1.00000
1.0	0.10127
2.5	0.08854
5.0	0.06645
10.0	0.06445

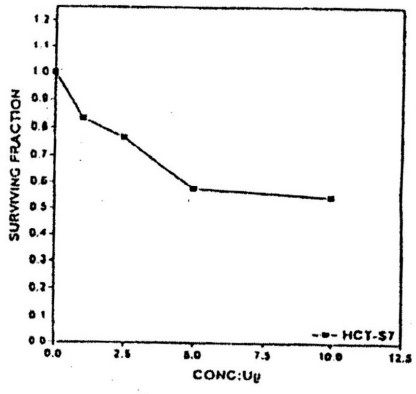
HEPG2



DRUG CYTOTOXICITY

CONC:Ug	HCT-S7
0.0	1.00000
1.0	0.83270
2.5	0.76734
5.0	0.57832
10.0	0.54719

HCT



Results

IC50: dose of the compound which reduces survival to 50%

Comp.	Cell line													
	HE-PG2	CA CO	HE LA	MC F7	H4 60	HCT 116	HE P2							
	IC50	IC10	IC50	IC10	IC50	IC10	IC50	IC10	IC50	IC10	IC50	IC10	IC50	IC10
11	0.6 µg			1.81 µg							-ve			

Comment

The tested enamino nitrile (11) showed this activity only at the specified concentrations and these cell lines. This compound has exhibit anticancer of liver and breast.

Table (1): Physical data for the synthesized compounds

Comp. No.	M.P. (°C)	Yield %	Molecular formula (Mol. wt.)	Analysis required/found					
				C	H	N	S	F	Br

4 2	182	85	$C_{15}H_{15}O_3NS$ (289.35)	62.2662.31	5.225.27	4.844.91	11.0811.12		
3	>300	75	$C_{15}H_{14}O_3NSBr$ (368.24)	48.9248.97	3.833.89	3.803.86	8.7008.65		21.6921.73

4	62	70	$C_{16}H_{15}O_2N_3S_2$ (345.44)	55.6355.69	4.374.41	12.16122.21	18.56188.61		
5	200	70	$C_{23}H_{21}O_3NS$ (391.49)	70.5670.61	5.405.45	3.573.61	8.198.23		

6 6	2 6 2	7 5	$C_{29}H_{28}O_3N_2S_2$ (516.68)	67.4167.47	5.4655.51	5.4255.47	12.1412.46		
7	1 1 5	7 5	$C_{18}H_{15}O_2N_3S$ (337.40)	64.0764.11	4.484.52	12.4512.49	9.509.57		

9	217	85	$C_{19}H_{15}O_2N_3S_3$ (401.39)	56.8556.89	3.763.81	10.4610.51	23.9623.99		
11	189	65	$C_{18}H_{15}O_2N_3S_2$ (369.46)	58.5158.55	4.094.13	17.3517.39	11.3711.39		

8 12	270	80	$C_{27}H_{19}O_2N_4S_2F$ (495.60)	65.4365.47	3.863.911	11.3011.35	12.9412.99	3.633.67	
13	250	85	$C_{25}H_{20}O_2N_4S_3$ (504.65)	59.5059.58	3.994.06	11.1011.15	19.0619.14		

15	>300	70	$C_{25}H_{20}O_2N_4S_3$ (504.65)	59.50 59.57	3.994.03	11.10 11.14	19.06 19.11		

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