

Synthetic of Some New Fluorine Compounds Bearing 1,2,4-Triazine Moieties and the Related Hetero-Polycyclic Nitrogen Systems as Pharmacological Probes-Overview

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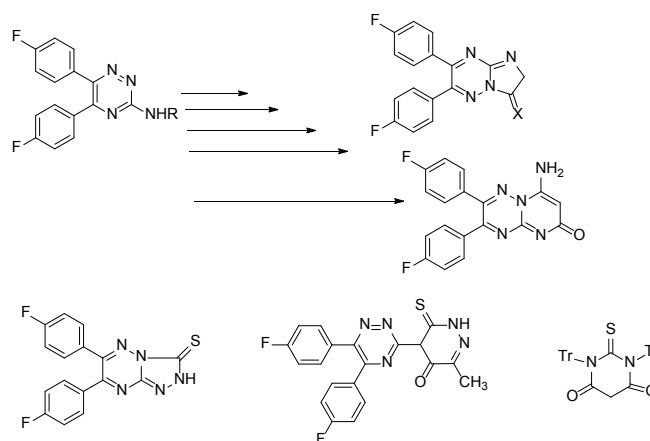


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Abstract

This overview summarizes recent advanced literature surveys on the synthesis of fluorine substituted 1,2,4-triazine containing various functional groups and/or the related hetero-polycyclic nitrogen systems have been reported. In addition, physical, chemical, and medicinal properties have been evaluated. The presence of fluorinated atoms often improves these properties with an increasing electronegativity. It, also, enhances the stability of formed carbanion and it improves the hydrophobic effects which have good biological activities.

Graph Abstract



Some important anti-HIV-1 and anticancer agent

Keywords

Design, Synthesis, Fluorinated 1,2,4-Triazino/1,2,4-Triazinone, Medicinal Properties

1. Introduction

Recently, fluorine substituted 1,2,4-triazine derivatives have been gathering considerable interest in various applications in pharmaceuticals activities and chemotherapy fields due to have a wide range of medicinal treatment as anti-HIV [1], anti-fungal [2], anti-cancer [3], anti-inflammatory [4], as cyclin-dependent kinases (CDK) [5] [6], anti-microbial activities [7], and antioxidant agents [8]. Most of the studies addressing synthesis and chemistry of fluorinated hetero-cyclic have been related to drug discovery research [9] [10]. It is interesting that replacing hydrogen and other functional groups with fluorine atoms can have a dramatic effect on the modulation of electronic, lipophilic, and steric parameters, all of which can critically influence both the pharmacodynamic and pharmacokinetic properties of drugs. Based upon these results, the present overview reports an important route of fluorine compounds substituted 1,2,4-triazine with the study of chemical reactivities and evaluation of the effects on the vital biological process.

2. Synthesis of 3-Amino/Mercapto-5,6-Difluoro-Substituted-1,2,4-Triazine

2.1. Synthesis

Musator *et al.* [11] synthesized 3-mercapto/methyl Thia-5,6-di(4'-fluorophenyl)-1,2,4-triazine (**1** and **2**) from refluxing 4,4'-difluorobenzene with thiosemicarbazide in glacial acetic acid followed by methylation via treated with MeI/NaOH/EtOH to yield **2** (**Scheme 1**). Similarly, refluxing 4,4'-difluorobenzil with aminoguanidine bicarbonate in n-butanol yielded 3-amino-5,6-di(4'-fluorophenyl)-1,2,4-triazine (**3**) (**Scheme 1**) [6].

2.2. Reactivity

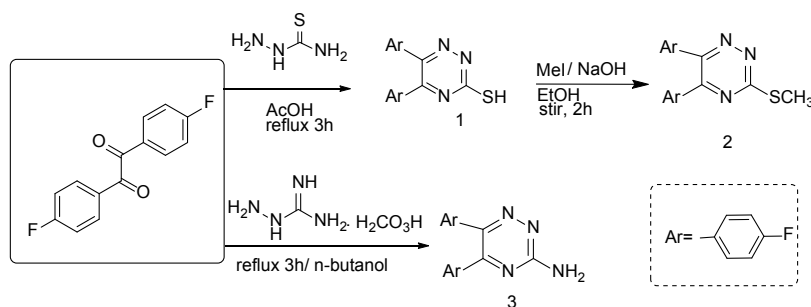
3-Amino-5,6-difluorophenyl-1,2,4-triazines are important intermediates in the synthesis of isolated and fused heterobicyclic nitrogen systems as biological agents. Thus, Makki *et al.* [6] synthesized some fluorinated 1,2,4-triazine bearing other heterocyclic moieties as cyclin dependent kinases (CDK) (**Scheme 2**). Thus, 3-amino-6,7-di(4'-fluorophenyl)-imidazo [3,2-*b*] [1,2,4]triazine (**4**) and 6,7-di(4'-fluorophenyl)-2,3-dihydro-3-oxo-imidazo [3,2-*b*] [1,2,4]-triazine (**5**) obtained from refluxing compound **3** with chloroacetonitrile and monochloroacetic acid in DMF respectively (**Scheme 2**) [6].

Cyclization reactions of 3-amino-1,2,4-triazine **3** with dimethyl malonate and

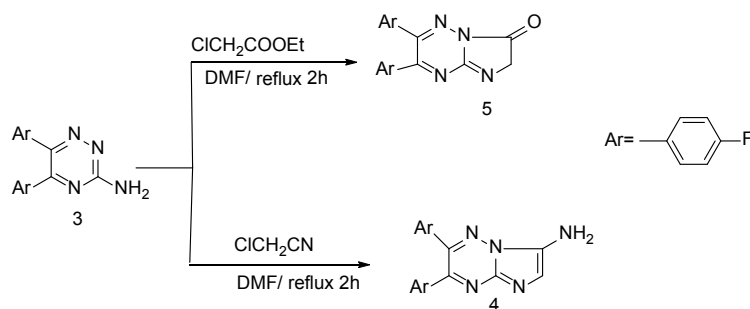
ethyl cyanoacetate in refluxing THF produced pyrimido [3,2-*b*] [1,2,4]triazin-2,4-dione (**6**) and 4-amino-pyrimido-[3,2-*b*] [1,2,4]triazine-2-one (**7**) respectively (**Scheme 3**) [6].

The possible mechanism for the formation of compound **7** is in shown in **Figure 1**. Also, the structure of **7** deduced from mass fragmentation pattern is reported **Figure 2**.

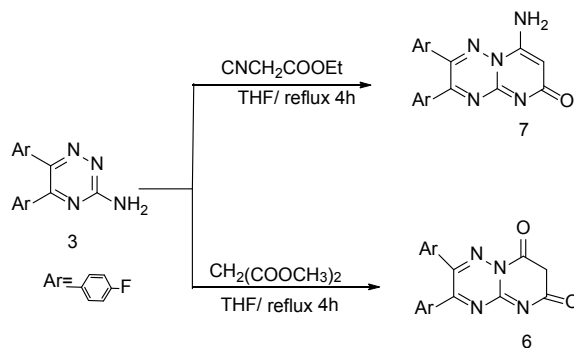
Semicarbazide and thiosemicarbazide derivatives used as starting material for the building of new hetero-polycyclic nitrogen systems as pharmacological probes [12] [13]. Thus, acylation of 3-amino-triazine **3** via treatment with ethylchloroformate in dry benzene and CS₂/KOH followed by hydrazinolysis (heated at reflux with hydrazine hydrate in EtOH) produced N⁴-(1,2,4-triazin-3'-yl) semicarbazide/thiosemicarbazide derivatives **10** and **11**, respectively (**Scheme 4**) [6].



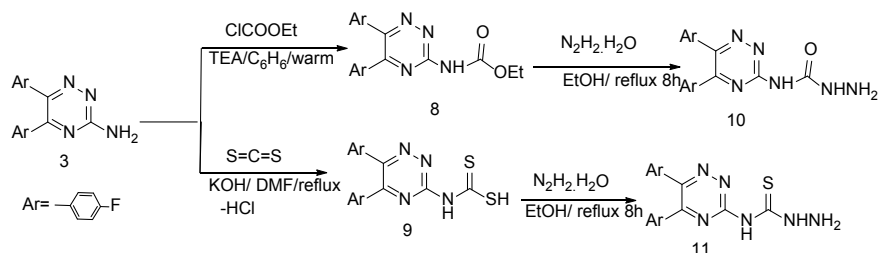
Scheme 1. Formation of compounds 1-3.



Scheme 2. Formation of compounds 4 and 5 from 3.



Scheme 3. Formation of compounds 6 and 7 from 3.



Scheme 4. Formation of compounds 8-11 from 3.

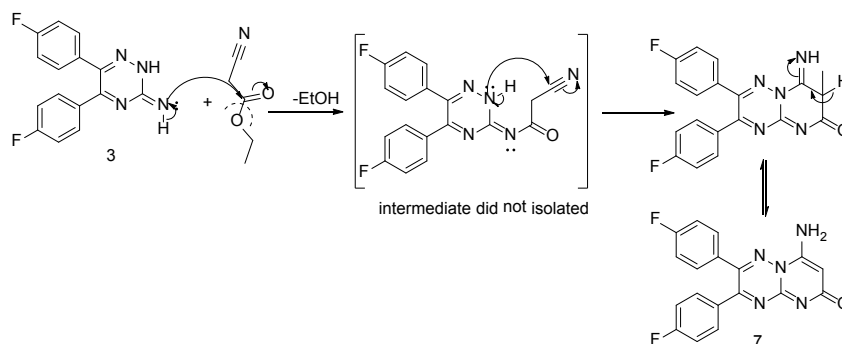


Figure 1. Formation compound 7.

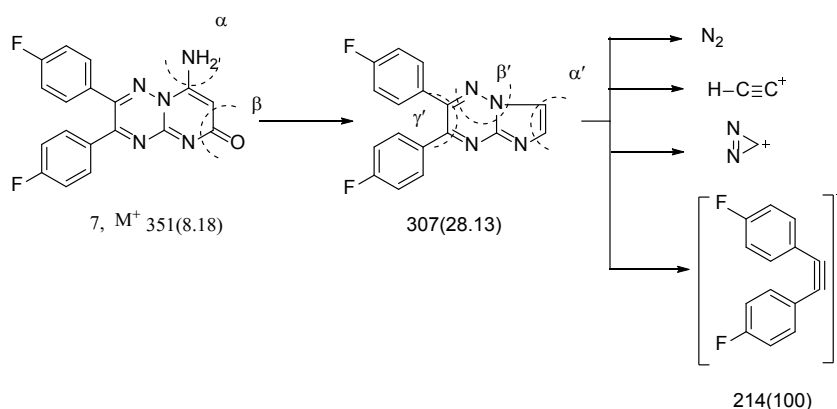


Figure 2. Mass fragmentation pattern of compound 7.

Under the experimental conditions, the ring closure reaction of compound 10 by refluxing with triethyl orthoformate, CS₂ (DMF) and sodium pyruvate (aq.NaOH) yielded the 1,2,4-triazolone 12 and 1,2,4-triazolthion 13 and the 6-azauracile 14, respectively (Scheme 5) [6].

The structure of compound 13 was deduced using the mass fragmentation pattern (Figure 3) [6].

Similarly, hetero-cyclization of compound 11 under the last same conditions and reagents lead to the direct formation of 1,2,4-triazol-3-thions 15 and 16 and/or 3-thioxo-4-[5,6-di(4'-fluoro-phenyl)1,2,4-triazin-3'-yl]-6-methyl-1,2,4-triazin-5-one (17), respectively (Scheme 6) [6].

On other hand, fully fluorinated thiobarbituric acids bearing 1,2,4-triazine moieties 19 obtained from the interaction between compound 3 with 9 in ref-

luxing EtOH to give N, N'-disubstituted thiourea **18**, which upon ring closure reactions with malonic acid in refluxing glacial acetic acid yielded the target **19** (Scheme 7) [8].

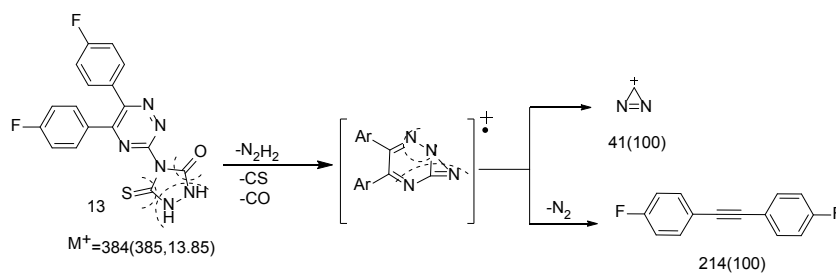
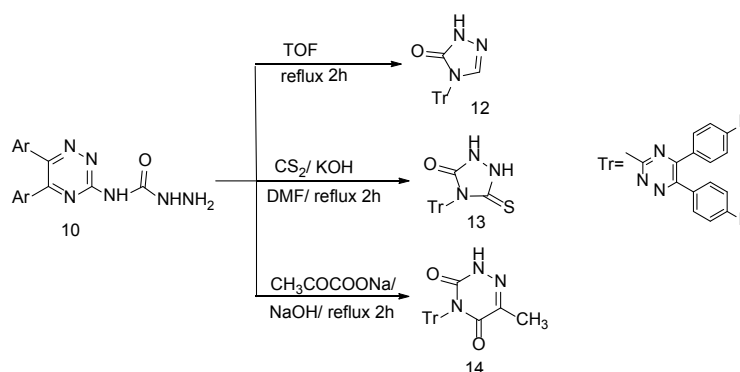
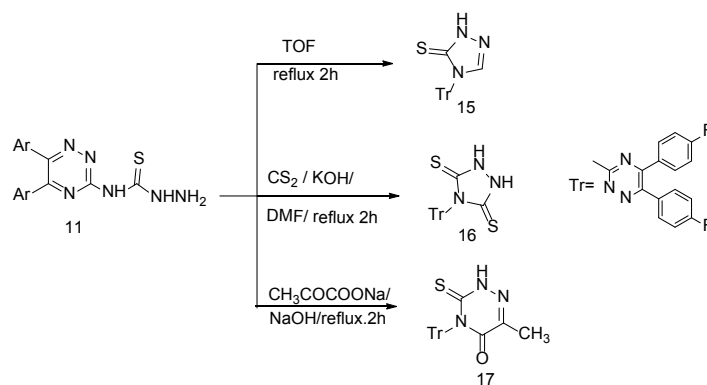


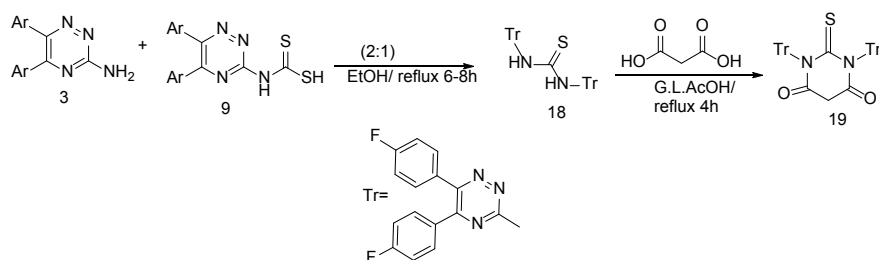
Figure 3. Mass fragmentation pattern of compound **13**.



Scheme 5. Formation of compounds **12-14** from **10**.



Scheme 6. Formation of compounds **15-17** from **11**.



Scheme 7. Formation of compounds **18** and **19**.

The CDK2 inhibitory activity of the compounds **3-9** evaluated in comparison with olomoucine as standard according the reported method [14], where the highly inhibitor effects increase in the order **11** > **13** > **16** > **17** > **3**. The compound **16** exhibit a good effect toward the tumor cells damage as the olomoucine. Also, the *in vitro* antitumor testing of the highly active compounds evaluated according the reported method [15] under different concentration. A sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth by determining GI_{50} , TGI, and LIC_{50} . Compound **11** showed the anti-cancer activity against non-small cell lung, renal, and breast cancer cell, while compound **13** exhibit anti-cancer of type leukemia and breast cancer cell, compound **16** showed anti-cancer activity against non-small cell lung cancer, finally, compound **17** exhibit anti-cancer of type breast cancer [6].

3. Synthesis of Fluorine Compounds Substituted Fused Hetero-Bicyclic Nitrogen Systems Containing 1,2,4-Triazines

3.1. Synthesis

Due to a highly resistance of microorganisms towards the anti-biotic uses, Aqlan *et al.* [16] synthesized new fluorine substituted pyrimido-1,2,4-triazinones as plant protection of wheat grain from fungi infection by using 2-hydrazino-4-(4'-fluorophenyl)-6-oxo-pyrimidine-5-carbonitrile (**20**) as a nucleophilic reagents attack of various functional reagents as electrophilic to produce the new fluorine compounds.

Cyclocondensation of 2-hydrazino-pyrimidinoe **20** with 1,2-bicarbonyl compounds such as sodium pyruvate/aq. NaOH or diethyl oxalate (THF) under refluxing 2h produced 8-(4'-fluorophenyl)-7-cyano-3-methyl-pyrimido [3,2-*c*] [1,2,4]triazin-4,6-dione (**21**) and 8-(4'-fluorophenyl) -7-cyano-1,2,3,4-tetra hydro pyrimido-[3,2-*c*] [1,2,4]triazin-3,4,6-trione (**22**), respectively (**Scheme 8**) [16]. The interaction between compound **20** with (E)4-aryl-2-oxo-but-3-eneoic acid in refluxing aq.NaOH, yielded 8-(4'-fluorophenyl)-7-cyano-3-styryl-1H-pyrimido [3,2-*c*] [1,2,4]triazin-4,6-diones (**23**) and not **24** (**Scheme 9**) [16].

Formal structure of compound **23** deduced from spectral measurements. Mass spectrometric study were recorded a molecular ion peak that the base peak **Figure 4** [16].

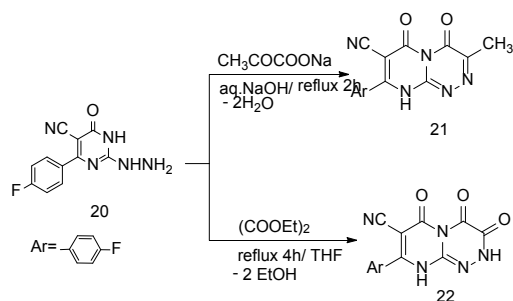
Due to the important properties of fluorinated heterocyclic substituted indole moieties for their applications [17] [18]. Thus, interaction between 2-hydrazino-pyrimidinone **20** and isatin in refluxing aq.NaOH or DMF yielded 8-(4'-fluorophenyl)-7-cyano-3-(2'-aminophenyl)-1H-pyrimido [3,2-*c*] [1,2,4]triazine-4,6-dione (**25**) or 11-(4'-fluorophenyl)-10-cyano-1H-pyrimido [3,2-*c*] [1,2,4]triazino-[6,5-*b*]indole(**26**), respectively (**Scheme 10**) [16].

A regioselective hetero-cyclization of 2-hydrazino-pyrimidinone **20** towards α -active electrophilic agents [19] [20] as monochloroacetic acid (aq.NaOH) and chloroacetyl chloride (DMF) under warming leads to the direct formation of fluorinate pyrimido-triazinones **27** and/or **28**, respectively (**Scheme 11**). Both

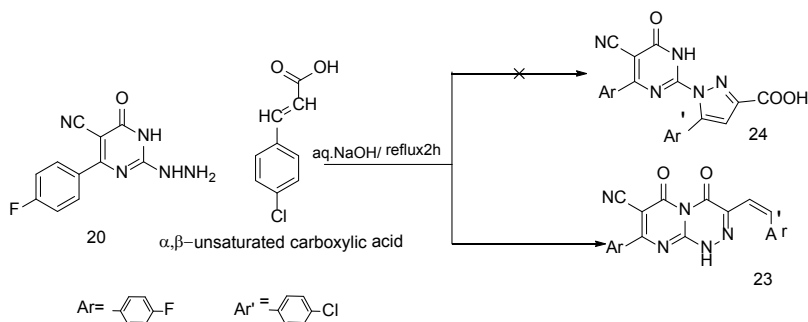
the compound **27** and **28** are considered an isomeric structure [16].

3.2. Reactivity

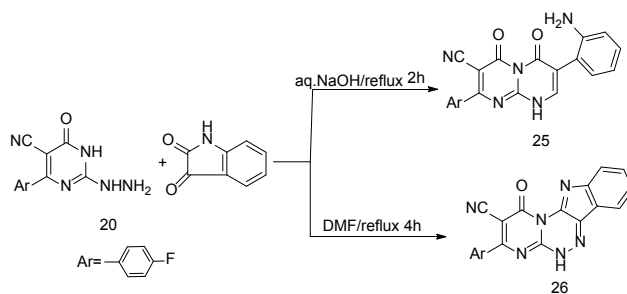
The mass fragmentation pattern of compounds **21** and **26** give us a good indication about their stability **Figure 5** and **Figure 6** [16], were the base peaks in these compounds are 95 (4-fluorophenyl) ions.



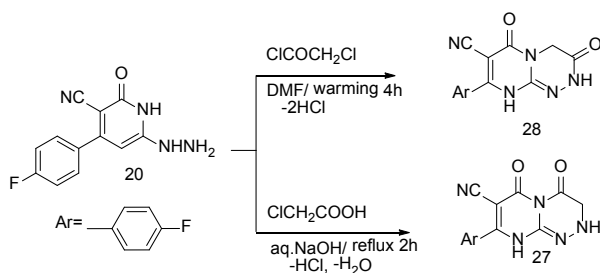
Scheme 8. Formation of compounds **21** and **22** from **20**.



Scheme 9. Formation of compound **23**.



Scheme 10. Formation of compounds **25** and **26** from **20**.



Scheme 11. Formation of compounds **27**, **28** from **20**.

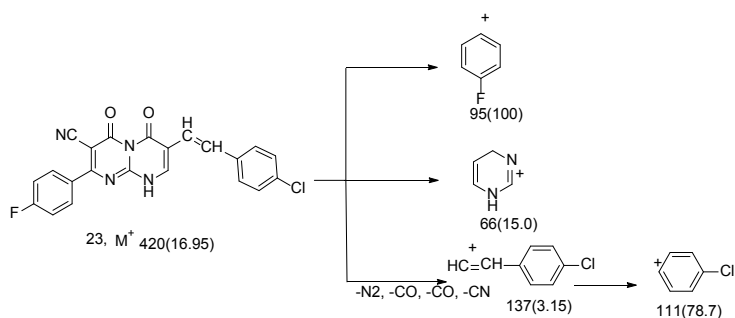


Figure 4. Mass fragmentation pattern of 23.

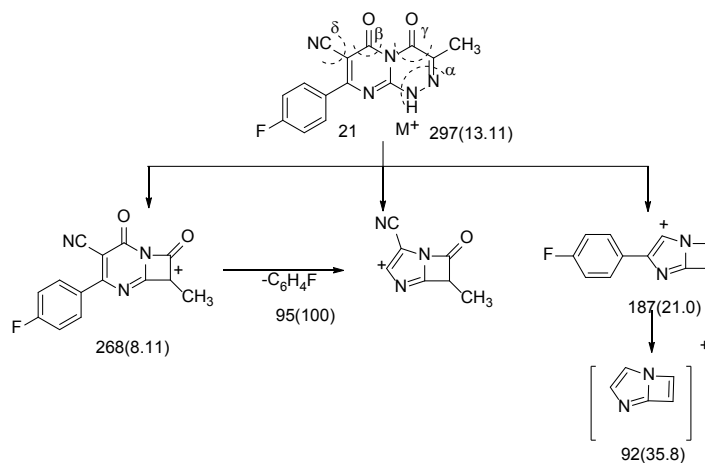


Figure 5. Mass fragmentation pattern of 21.

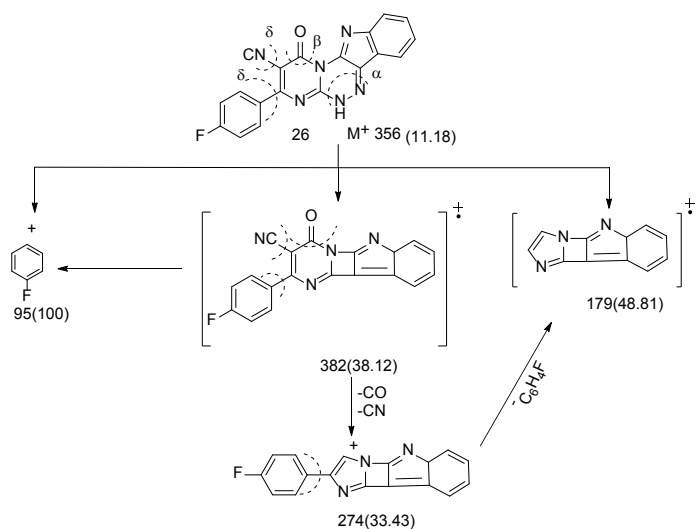


Figure 6. Mass fragmentation pattern of 26.

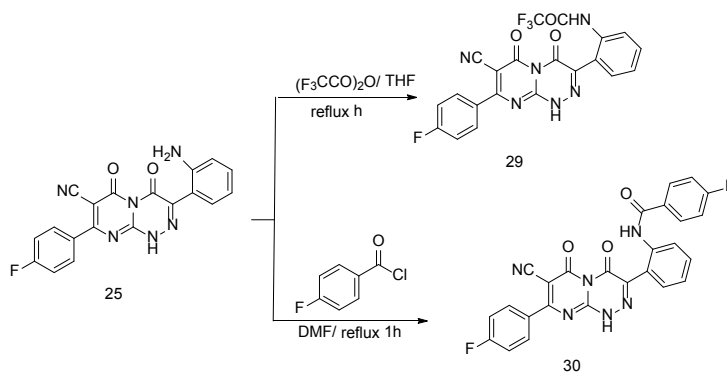
The presence of a free amino group in the structure of **25** was established from Fluoroacylation by warming with hexafluoro-acetic anhydride (DMF) or fluoro-arylation by warming with 4-fluoro-benzoyl chloride (DMF), afforded the N-(trifluoroacetamido) **29** or N-(4'-fluoro benzamido) derivatives **30**, respectively (**Scheme 12**) [16].

Oxidation of **27** and **28** via refluxing with $\text{Fe}_2(\text{SO}_4)/\text{CH}_3\text{OH}$ yielded the tautomeric structures **31** and **32**, respectively (**Scheme 13**) [16].

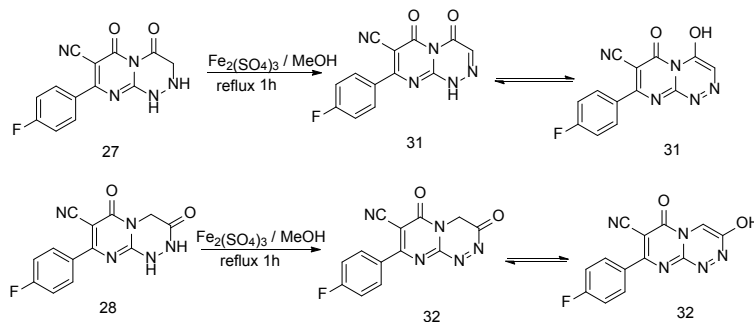
The obtained compounds **21-32** evaluated both *in vitro* and *in vivo* of anti-fungal activity by inhibition of fungal mycelial growth of *Alternaria alterata*, *helimen thosporium sativum* and *Fusarium moniliform* according the reported methods [21] [22] [23], where the compounds **23**, **29** and **30** exhibit a high fungal toxicity activity. Prevention of blue mold development indicate the action of these compounds on the decay control on rind discs, were only the compounds **21** and **23** gave a good control at concentration at 500 mg/cm^{-1} against *Alternaria alterata*. The best germination (80% - 90%) was achieved by treating the seeds with a solution containing 1000 mg/ml of the compound **23** followed by **29** under the same concentration (59% - 70% germination) [16]. Similarly, the design, synthesis and molluscicidal activity of new phosphorus compounds bearing fluorine substituted 1,2,4-triazolo [5,1-c] [1,2,4]triazine derivative reported by Abdel-Rahman *et al.* [24].

3.3. Synthesis

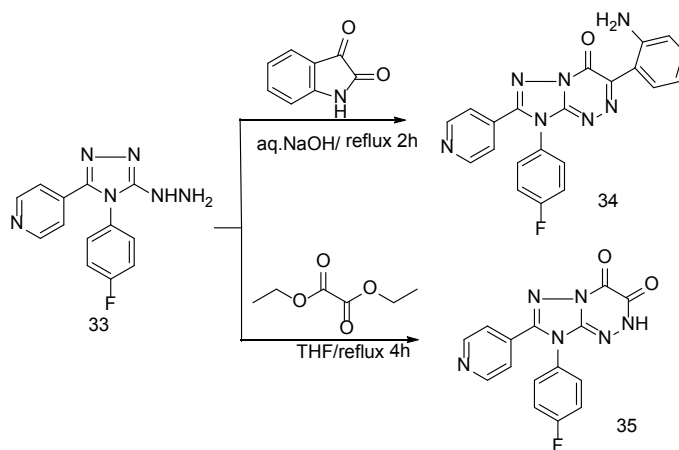
Refluxing 3-hydrazino-4-(4'-fluoro phenyl)-5-(pyridine-4'-yl)-1,2,4-triazole (**33**) with isatin in aq.NaOH or with diethyl oxalate in THF produced 3-(2-amino-phenyl)-8-(4'-fluorophenyl)-7-(pyridine-4'-yl)-1,2,4-triazol [5,1-c] [1,2,4]triazin-4(8H)-one (**34**) or 8-(4'-fluorophenyl)-7-(pyridine-4'-yl)-2,4-dihydro [1,2,4]-triazol [5,1-c] [1,2,4]triazin-3,4-dione(**35**), respectively (**Scheme 14**) [24].



Scheme 12. Formation of compounds 29 and 30 from 25.



Scheme 13. Oxidation of compounds 27 and 28.



Scheme 14. Formation of compounds **34** and **35** from **33**.

3.4. Reactivity

Phosphorylation of both compounds **34** and **35** by warming with chloro-diphenyl phosphate in the presence of DMF afforded the N-(diphenyl phosphiteamino) **36** and **37**, respectively (**Scheme 15**) [24].

The stability of compound **37** is indicated by the mass fragmentation pattern in **Figure 7**.

Compound **36** and **37** can be used as molluscicidal agents against the snails which cause the disease of Bilharziasis according to the reported method [24], where compound **37** exhibits higher activity than **36** in comparison with Bayluscids as a standard control (**Table 1**) [24].

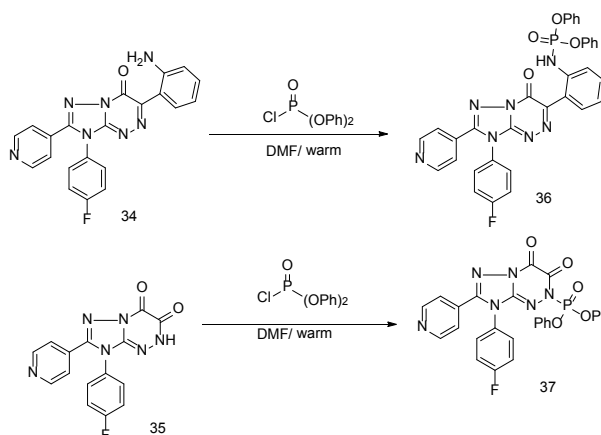
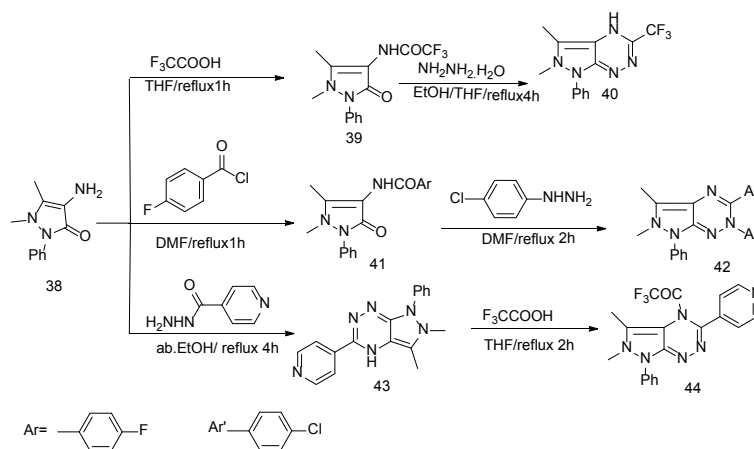
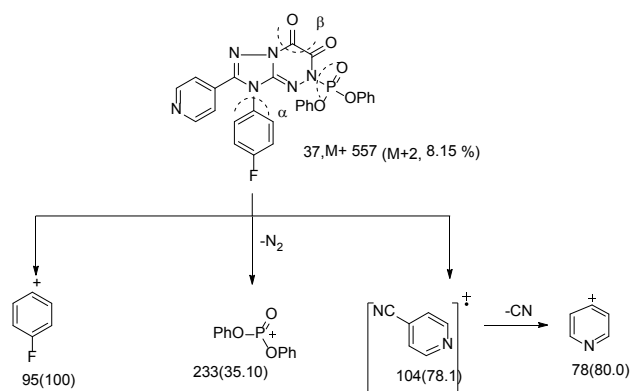
4. Synthesis of Fluorine Substituted Pyrazolo [4,3-e] [1,2,4]Triazines as Purine Analogues as (Condensed Systems)

4.1. Synthesis

Fluoroacylation of 4-aminoantipyrine (**38**) by warming with trifluoroacetic acid in THF yielded the N-trifluoroacetyl derivative **39**, which upon heterocyclization by refluxing with hydrazine hydrate in abs. EtOH produced 2,3-dimethyl-1-phenyl-4H-5-trifluoromethyl-pyrazolo [4,3-e] [1,2,4] triazine (**40**), arylation of **38** by warming with 4-fluorobenzoyl chloride in DMF produced the N-aryl amino **41**. Ring closure reaction of **41** with aryl hydrazine in refluxing DMF gave 2,3-dimethyl-5-(4'-fluorophenyl)-6-(4'-chlorophenyl)-1-phenyl-pyrazolo [4,3-e] [1,2,4] triazine (**42**) (**Scheme 16**) [25]. Similarly, cyclocondensation of **38** with acid hydrazide in refluxing DMF yielded the pyrazolo-triazine **43**, which on fluoroacylation produced N-trifluoroacetyl **44** (**Scheme 16**). The formation of **42** from **38** is shown in (**Figure 8**). Also, mass spectroscopy study of compound **44** showed the molecular ion peak at low % with a base peak at m/z 198 (100%) attributed to $C_{12}H_{12}N_3^+$ as **Figure 9** [25].

Table 1. The mortality of snails at different concentrations.

Mortality of snails at different concentration			
Compound No.	25 ppm	50 ppm	100 ppm
36	75	80	90
37	80	82	92
Bayluscide	100	100	100

**Scheme 15.** Formation of compounds 36 and 37.**Scheme 16.** Formation of compounds 39-44 from 38.**Figure 7.** Mass fragmentation pattern of 37.

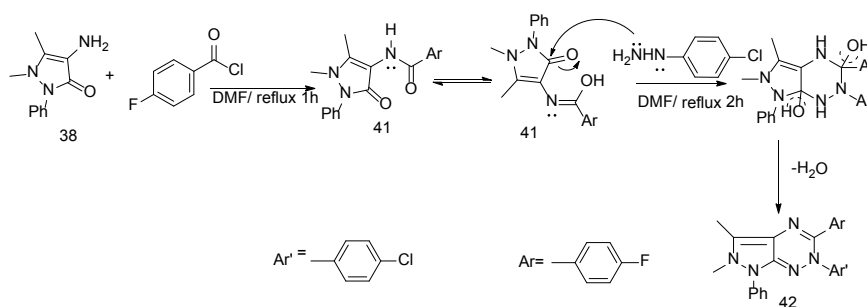


Figure 8. Formation of compound 42 from 38.

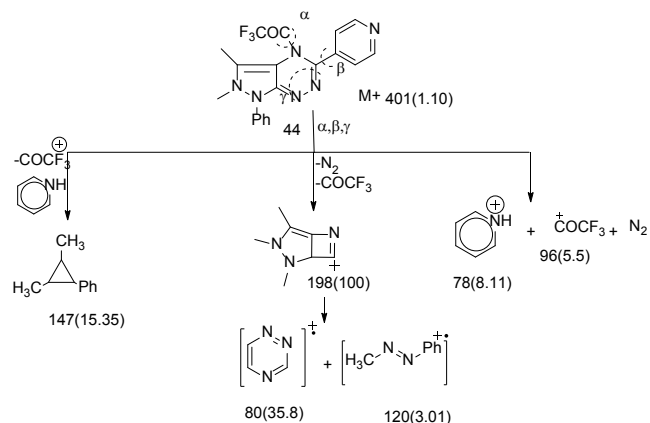


Figure 9. Mass fragmentation pattern of compound 44.

The addition of aryl isothiocyanate to compound 38 in warming DMF, yielded the *N,N'*-disubstituted thiourene 45, which upon hydrazinolysis in refluxing ethanol, produced 2,3-dimethyl-1-phenyl-4*H*-5-aryl amino-pyrazolo [4,3-*e*] [1,2,4]triazine (46), while addition of CS₂ in aq.KOH to 38, followed by hydrazinolysis gave *N*⁴(substituted)thiosemicarbazide 47. Self-condensation of 47 lead to the formation 2,3-dimethyl-1-phenyl-4,5,5,6-tetrahydro-5-thioxo-pyrazolo [4,3-*e*] [1,2,4] triazine (48) **Figure 10**. Compound 48 also obtained [25] directly from refluxing 38 with thiosemicarbazide in acetic acid (**Scheme 17**). Formation of compound 48 from 38 may be take's place via the addition reaction between an amino-group of 38 and highly positive Carbone atom of CS₂ followed by hydrazinolysis 47 and finally cyclocondensation via carbonyl group as shown in **Figure 10**.

Also, 2,3-dimethyl-1-phenyl-4,5,5,6-tetrahydro-5-oxo-pyrazolo [4,3-*c*] [1,2,4]-triazine (50) was produced from treatment of compound 38 with ethylchloroformate in warming C₆H₆-TEA followed by hydrazinolysis in refluxing THF (**Scheme 18**) [25].

It is interesting that, addition compound 38 as nucleophilic agents to π -acceptor electrophilic as cyanamide in refluxing EtOH-piperidine as catalysis yielded the guanidine derivative 52, which on hydrazinolysis in DMF afforded 5-amino-2,3-dimethyl-1-phenyl-4*H*-pyrazolo [4,3-*e*] [1,2,4]triazine (53). Compound 53, also isolated from addition of H₂NCN into compound 38 to give the amino-nitrile 54, followed by hydrazinolysis (**Scheme 19**) [25].

4.2. Reactivities

Fluoroacylation of compounds **43**, **50** and **53** by warming with trifluoroacetic acid in THF lead to the isolation of *N*-trifluoroacetyl derivatives **44**, **51**, and **55**, respectively (**Scheme 20**) [25].

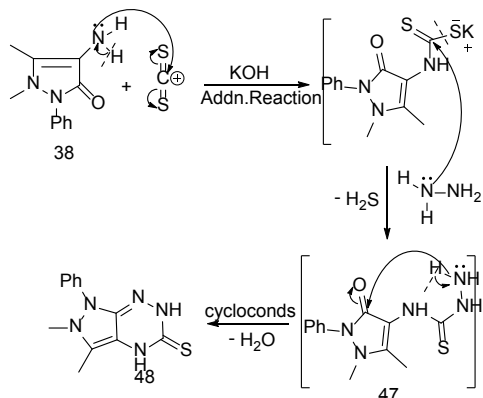
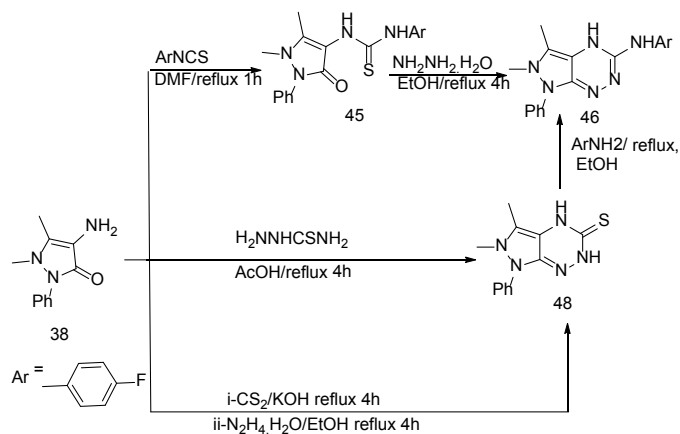
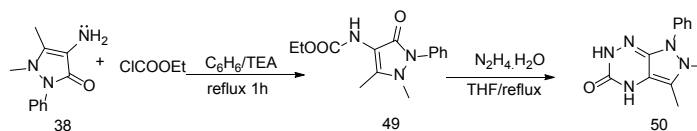


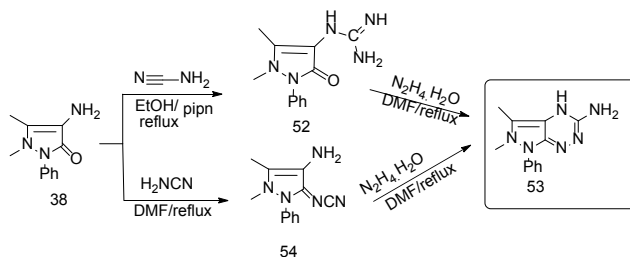
Figure 10. Formation of compound **48** from **38**.



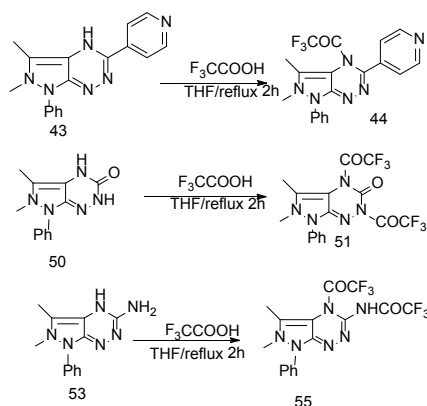
Scheme 17. Formation of compounds **45**, **46** and **48** from **38**.



Scheme 18. Formation of compounds **49** and **50**.



Scheme 19. Formation of compounds **52-54**.



Scheme 20. Formation of compounds 44, 51 and 55.

The enzymatic properties of the synthesized compounds **40-55** were evaluated against purine metabolic enzymes at concentrations of 30 - 500 μM [26] [27]. The hexafluoroacetyl derivatives **51** and **55** were the strongest inhibitors with IC_{50} of 30 - 40 μm followed by trifluoroacetyl **44**. Non-fluorinated derivatives exhibit much moderate to lethal inhibitor activity towards *E. coli* PNP an enzyme [25].

5. Synthesis and Reactivity of Fluorine Compounds Substituted Hetero-Polycyclic Nitrogen Systems Containing 1,2,4-Triazino-Indole Moiety (Condensed Skelton)

Joshi *et al.* [28] reported some fluorine compounds containing 3-dialkyl aminoethyl thio-5-morpholino-methyl-1,2,4-triazino [5,6-*b*]indoles as having anti-bacterial, antifungal, and anti-viral activities (**Figure 11**). Also, Abdel-Rahman *et al.* [18] synthesized new fluorine substituted 3-amino-1,2,4-triazino-[5,6-*b*]indoles derived from sulfa-drugs and fluorinated reagents as photochemical probes agents for inhibition of vitiligo disease. On other hand, novel herbicidal 3-dimethylamino-4*H*-1,2,4-triazino [5,6-*b*]indoles obtained by Mizutani *et al.* [29] (**Figure 11**) [30] [31] [32]. Recently, fluorine substituted 3-amino-1,2,4-triazino-indoles and/or 3-amino-imidazol-1,2,4-triazino-indoles have been used as anti-inflammatory agents [30] [31].

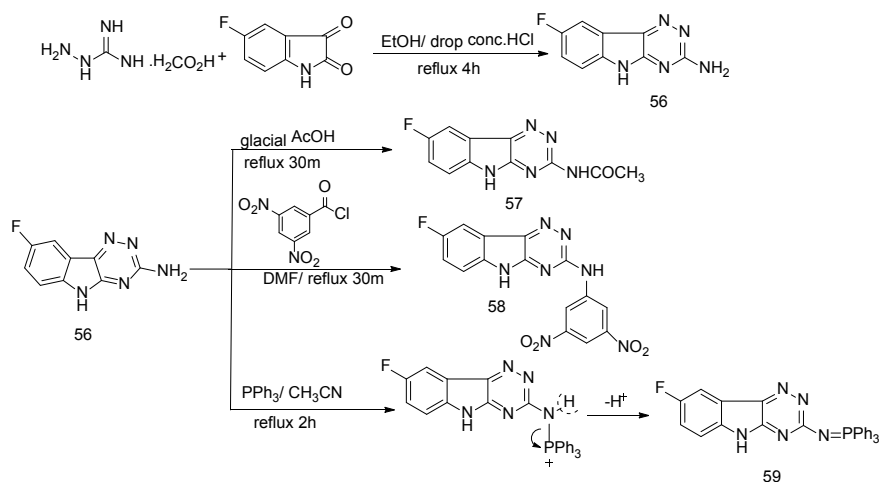
3-Amino-8-fluoro-5*H*-1,2,4-triazino [5,6-*b*] indole (**56**) [30] (**Scheme 21**), was used to obtain a various of new fluorine compounds **57-61** via the treatment of **56** with different electrophilic reagents in various media. Thus, acylation of **56** by warming with glacial AcOH for short time yielded 3-*N*-acylamino-derivative **57**, while aroylation of **56** via warming with 3,5-dinitrobenzoyl chloride in DMF produced the benzamido derivative **58**. Refluxing **56** with PPh_3 (similarly as Wittigs reaction) afforded the phosphiimino-derivative **59** (**Scheme 21**).

Most of alkylated amino-1,2,4-triazino [5,6-*b*] indoles obtained exhibit a wide range of biological activities [31] [32]. Similarly, treatment of compound **56** with MeI (1%aq.KOH. stirring at R.T), monochloroacetic acid (DMF), or chloroaceto-

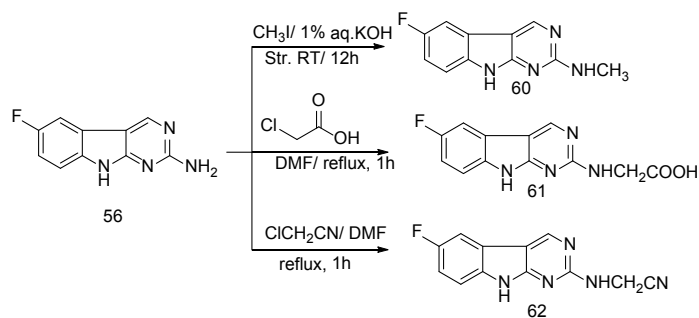
nitrile (DMF) lead to the direct formation of 3-N-alkyl derivatives **60-62** (Scheme 22) [30].

Thiazolidin-4-one derivatives obtained exhibit a highly biological, pharmacological, and medicinal activities [33] [35]. Thus, condensation of compound **56** with 4-chlorobenzaldehyde in AcOH under refluxing yield the Schiff base **63**, which upon cycloaddition with thiolactic acid in refluxing 1,4-dioxane, afforded 2,3,5-trisubstituted thiazolidine-4-one (**64**) (Scheme 23) [30]. The formation of **64** is shown in Figure 12.

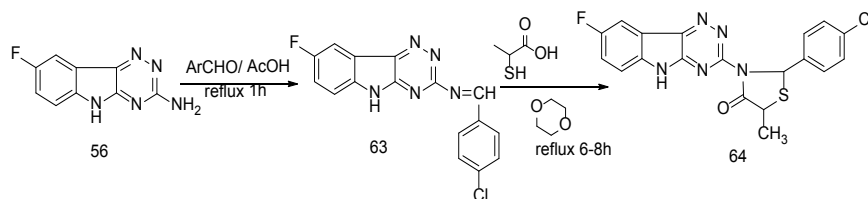
The former structure of **64** deduced from the correct elemental analysis and spectral measurements. The mass fragmentation pattern of **64** gives us a good indication about that stability Figure 13 [30].



Scheme 21. Formation of compounds 57, 58 and 59.



Scheme 22. Formation of compounds 60-62.



Scheme 23. Formation of compounds 63 and 64.

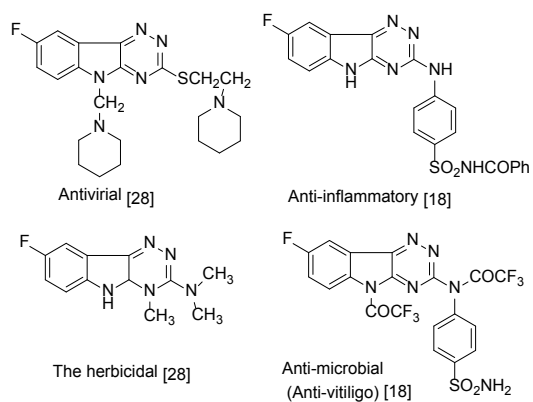


Figure 11. Some important medicinal compounds.

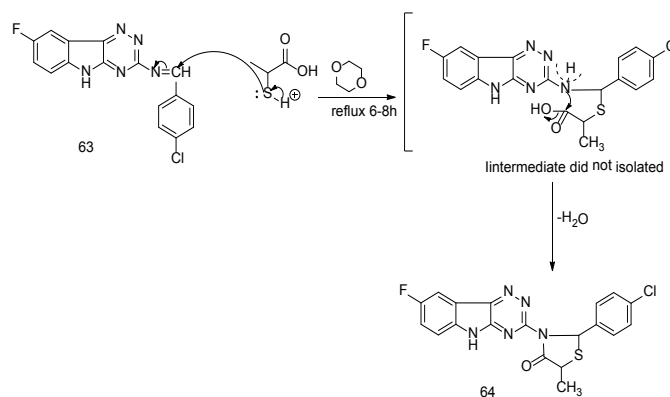


Figure 12. Formation of compound 64 from 63.

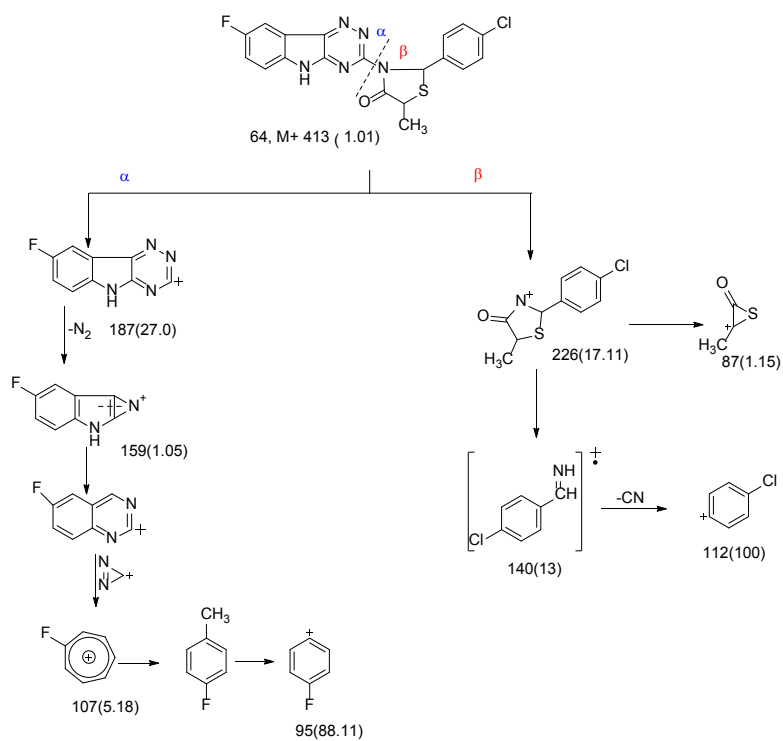


Figure 13. Mass fragmentation pattern of 64.

It is interesting that the interaction between 3-amino-8-fluoro-5H-1,2,4-triazino [5,6-*b*]indole (**56**) and chloroacetonitrile in refluxing DMF lead to the direct formation of 3-amino-7-fluoro-10H-imidazo [3,2-*b*] [1,2,4]triazino [5,6-*b*]indole (**65**) (**Scheme 24**) [30]. Formation of **65** may be a simple nucleophilic attack of NH_2 to more E^+ center followed by cycloaddition reaction (**Figure 14**) [30]. Similarly, acylation and aroylation of compound **65** under the normal condition (RCOOH and ArCOX) produced the 3-*N*-acyl/aroyl amino-imidazo [3,2-*b*] [1,2,4]triazino [5,6-*b*]indoles **66** and **67**, respectively (**Scheme 24**) [30].

Finally, alkylation of **65** via treatment with MeI in aq.KOH at room temperature and/ or with chloroacetic acid in refluxing DMF yielded 3-*N*-alkylamino-derivatives **68** and **69**, respectively (**Scheme 25**). Decarboxylation of **69** by warming with aq.KOH gave 3-methylamino-imidazo [3,2-*b*] -1,2,4-triazino [5,6-*b*]indole (**68**). The reaction of **65** with PPh_3 in CH_3CN yielded the phosphiimino **70** derivative (**Scheme 25**) [30]. The formation of compound **70** is indicate in **Figure 15** [30].

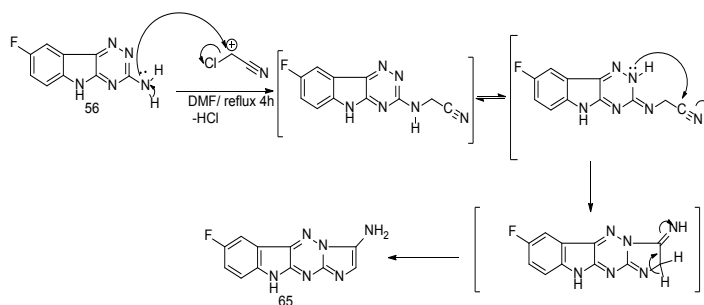


Figure 14. Formation of compound **65** from **56**.

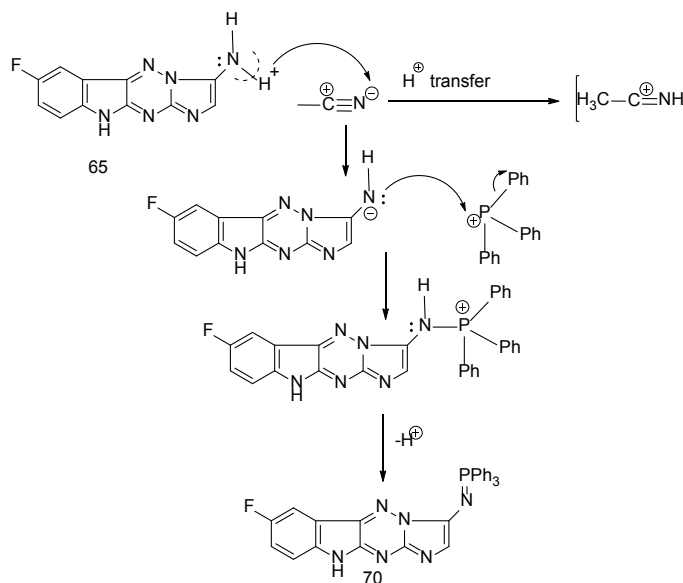
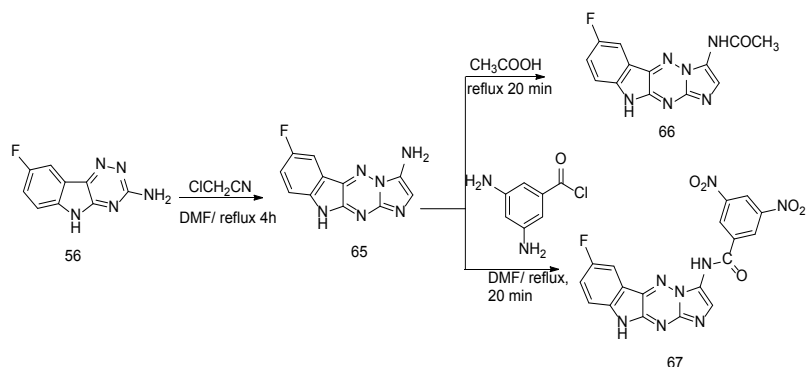
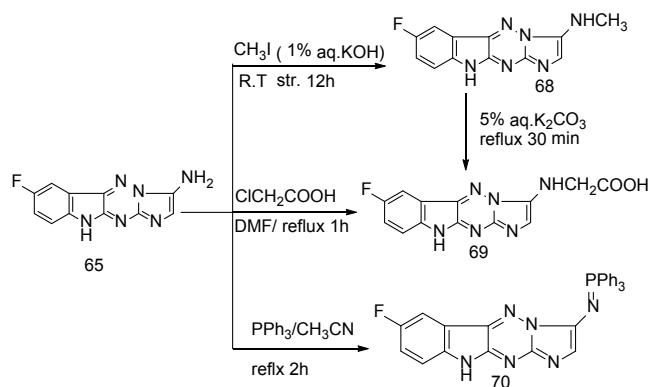


Figure 15. A possible route to formation of compound **70** from reaction of **65** with PPh_3 in CH_3CN .



Scheme 24. Formation of compounds 66 and 67.



Scheme 25. Formation of compounds 68-70.

The introduction of fluorine atoms to 1,2,4-triazine derivatives often enhance and improve those properties, especially the medicinal and pharmacological field [1] [31]-[36]. Recently, the high resistance of microbes towards most drugs and antibiotics, is driving an urgent need for the synthesis of new highly bioactive systems in view of control on these resistant [37] [38] [39]. Thus, all synthesized fluorine compounds **56-69** evaluated as anti-inflammatory agents by using the standard indomethacin drug as standards, according the reported method [30], the activities were ranked as **65** > **56** > **64** > > **58** > **67** > **60**. Both the compounds **56** and **65** which contains a fluorine atom and an amino-group at the end of presence systems form a type of bio-conjugated systems. Also, a higher activity of compound **64** may be the formation of type combination between the thiazolidine-4-ones, and fluorine, chlorine bonded the terminal of systems [30].

6. Important and Applications

Fluorine containing 1,2,4-triazine moieties are high biological activity. Thus, the introduction of fluorine atoms to isolated, fused, and condensed 1,2,4-triazine systems can produce new bioactive targets depend on the position and magnitudes of total change. Most fluorinated 3-amino- or 3,5-diamino-6-aryl-1,2,4-triazines exhibit an anti-inflammatory activity exceeding that of lamotrigine drug as **Figure 16** [40].

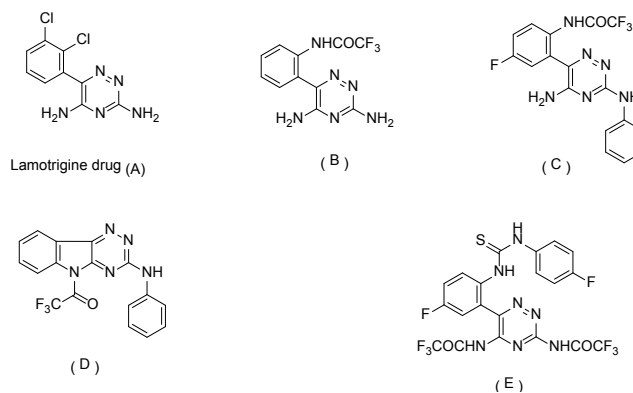


Figure 16. Some important medicinal compounds.

Most of fluorinated 1,2,4-triazin-5-one moieties display anti-HIV activity [1] [5]. Also, some fluorine-substituted with phosphorous-1,2,4-triazines exhibited an important antioxidant activity [8]. As well as mostly, fluorine substituted 3-thioxo-1,2,4-triazinones showed a potential inhibitor as cyclin depend kinas (CDK2) for tumor cell damage [5] [6]. Recently, some fluorinated fused and isolated 1,2,4-triazines systems have been reported to have biocidal affect as molluscicidal agents against some snails [24]. In addition, many new fluorine compounds substituted by some or more heterobicyclic moieties, especially 1,2,4-triazine moiety, showed a wide range of antimicrobial activity [1] [7] [9] [10] [16] [18] [33]. Finally, some fluorinated 1,2,4-triazinones synthesized use as enzymatic affects towered some fungi [2] [9] [13] [16] [25].

7. Conclusion

A series of various fluorine compounds substituted with 1,2,4-triazine moieties have been developed by various routes. The results of these targets were characterized physically, chemically, or both, together with evaluations of the pharmacological activities. The introduction of fluorine atoms to heterocyclic nitrogen systems mostly enhances and improves the physical, chemical, and biological properties. In view of the fluorinated 1,2,4-triazine derivatives obtained, most have potentially beneficial applications for our life to treat various diseases such as anti-inflammatory, antimicrobial, or anti-HIV1 agents, or as cyclin dependent kinase inhibitors for tumor cell damage of DNA moiety. Hopefully, the present overview contributes an explanation of how new fluorine compounds bearing 1,2,4-triazine moieties and the related hetero-polycyclic nitrogen systems are formed and used.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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