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Synthesis and characterization of mixed Amides-Imines and Amides-Azo Compound derived from Chrysanthemic acid and trimethoprim and study their biological activities

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imines,
amides,
azo compound.

ABSTRACT

Chrysanthemic acid, Trimethoprim, amides, Imines and azo compound : all found to have enormous biological activities in different directions such as medical , pharmaceutical pesticidal …etc. Accordingly combination of these functional in on compound expected to enhances their activities. Therefore mixed amides – imines and amides – diazo derived from trimethoprim and chrysanthemic acid, have been prepared by reaction of equimolar amount of these compound to form the corresponding mono amides , which on treatment of the remaining amino group of the trimethoprim with some aromatic aldehydes give the corresponding imines ; or diazo compounds on reaction with nitrous acid followed by reaction with aromatic phenols and naphthols . The structures of these derivatives were confirmed by their physical properties and spectroscopic techniques such as FT-IR ; ^{1}Hnmr and mass spectrometry for selected compound. In addition the biological evaluation of the synthesized compound have been studied through the investigation of its capacity to scavenge the free radical (DPPH·) to give an inhibition at 50% concentration (IC_{50}) , using the butylated hydroxyl toluene (BHT) as a control. This study reveals the highest scavenging for the azo derivatives.

Introduction

Amides, imines, azo-compounds, trimethoprim and chrysanthemic acid , all found enormous uses in many fields, such as medicinal, pharmaceutical, agricultural ..etc. due to their biological activities[1-3]. Therefore they played a vital role in our life.

Amides is an organic compounds with a carbonyl carbon bonded to the amine group through the nitrogen atom. Amides were classified to 1º, 2º ,3º according to the type of the amine bonded to the carbonyl group. It can be aliphatic, aromatic cyclic depending on the groups connected to the nitrogen [1].

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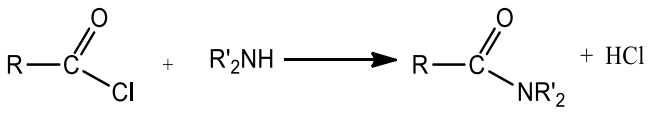
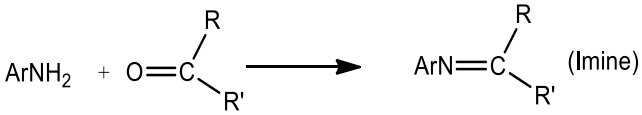
The amide bonds play an important and active role in many biological systems. It is associated with protein and peptide linkage, in addition to its medicinal importance. More than 25% of medicine contain an amidic bonds such as lisinopril[4], Deltazem [5] which are used for the treatment of hypertensive and cardiovascular problems[6,7]. Most amide derivatives have a vital role in drugs as active ingredients or antibiotics such as anticancer(8), antibacterial(9), antifungal .. etc.

The most known method for preparing amides is the (Schotten- Baumann) coupling between acid chlorides and amines[10]

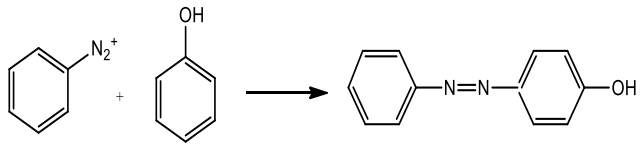


Imines or Schiff's bases are nitrogenous compounds analogous to aldehydes and ketones in which the carbonyl group replaced by azomethine . Although the later less reactive due to the less electronegativity of nitrogen atom compare with oxygen. It considered as important intermediates in the preparation of a biologically active compounds (β-Lactams) ;[11] in addition to its use as antibacterial, antimicrobial , anti HIV[12,13] and antifungal [14].

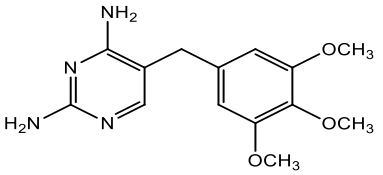
They were first prepared by the German scientist Schiff in 1864 , by condensation of aliphatic or aromatic 1° amines or other amino acids with aliphatic or aromatic aldehydes or ketones.



Azo compounds are known by the general formula R-N=N-R' where R and R' aromatic or aliphatic. They give vivid and brightly color which absorb in visible or ultra violet region. Some azo compounds such as methyl-red or methyl-orange are used as indicators in acid-base titration . Azo compounds gained an important role through their uses in medicinal area as antibacterial, antitumor, antibiotic ….etc. Aromatic azo compounds which are more stable can be synthesize by using an azo coupling reaction by electrophilic attack of the diazonium salt on the other activated aryl rings such as phenols naphthols or aniline derivatives . This reaction is used to prepare symmetric and asymmetric azo compounds [15] .



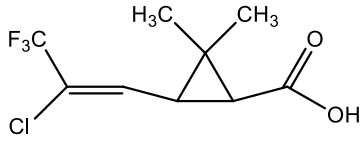
Trimethoprim is a diamine derivative of heterocyclic pyrimidine ring structure below:



(Trimethoprim)

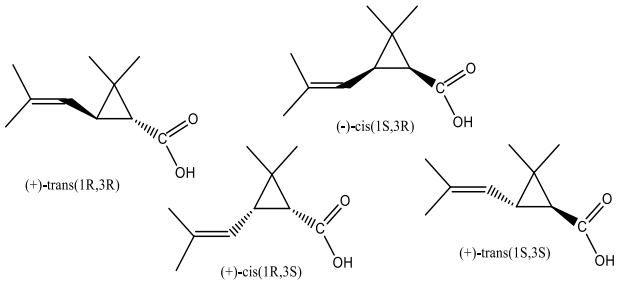
It is widely used as antimicrobial, antibacterial, antibiotic which inhibit the dihydro folate reductase (DHFR) enzyme[16,17]

Chrysanthemic acid is an organic carboxylic acid with cyclopropane ring moiety connected to the carboxyl group and also to a carbon- carbon double bound . These functional groups give the carboxylic acid and the alkene properties [18].



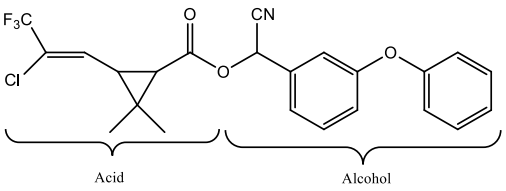
(Chrysanthemic acid)

The acid with two stereogenic centers at C1 and C3 to form four stereoisomers; two cis and two trans isomers, as shown below :



The (+)-trans (1R,3R) is the most active among the other isomers and it gives the acid its biological activity.

The acid represent the main effective functional site of the active ingredient ester (Lambda-cyhalothrine) used for synthetic and natural pyrithroidal insecticide.



(Cyhalothrine)

λ-cyhalothrine is the fourth generation for the synthetic pyirthroid insecticide used in agriculture, public area and household formulation in a very low concentration[19] comparing with other families of

insecticides, due to their high toxicity to insecticide but safe for mammalian [20].

The target is to synthesize compounds which include most of the previously mentioned functional sites to enhance the biological activity of these

The next step of this research was reaction of the remaining group of mono amide above with aromatic aldehydes and ketones to form amide-imine derivatives of trimethoprim and chrysanthemic acid, or converting the amine group to diazonium salt through the reaction with nitrous acid , then coupling with phenols or naphthols to form amides-azo compound. The third step was characterization of the prepared compounds by available spectroscopic methods such as FT-IR , ^{1}Hnmr , and GC-MS. Finally evaluating the biological activities of the selected compounds to determine.

2- Materials and instrumentation

2.1 Materials

All solvents and reagents were used without further purification. Phenol, α-naphthol, β-naphthol, acetophenone, benzophenone, HCl, $NaNO_2$ were supplied from BDH. 3-hydroxy benzaldehyde; 4-dimethyl amino benzaldehyde from Fluka and benzaldehyde from Merck. Others such as trimethoprim from samara drug industry. λ-cyhalothrine from local pesticide company.

2.2 Instrumentation:

Melting points were measured by electro thermal apparatus (uncorrected), FT-IR spectra were recorded by Fourier transformer infrared spectrophotometer model tensor 27, Brocker company (Germany). All IR spectra in arrange 400-4000 cm^{-1}, using KBr disk.^{1}Hnmr spectra were recorded on 300 MHz using Brucker instrument ultra-shield, using DMSO as a solvent. Mass spectra were obtained from GC-MS model GC-MS QP 2010 SE from Shimadzu (Japan). Direct inlet of the samples. TLC strips were used to determine the purity and the progress of reaction. These were supplied from local market.

derivatives . Therefore the first stage was to prepare the mono amide of trimethoprim with chrysanthemic acid in equimolar ratio, and displacement of alcohol in λ-cyhlothrine with trimethoprim.

3. Methods:

3.1 Preparation of the mono amide of chrysanthemic acid

Mono amide was prepared according to the literature procedure[8] with some modification, by reacting an equimolar amount of trimethoprim and λ-cyhalothrine (0.01 mole) each; in 40 ml of 4% sodium hydroxide. The mixture was reflux at 200° C for 1.5 hr., during which a pale yellow precipitate was formed. Filtered washed with ether and recrystallized from ethanol. m.p., and other physical properties, FT-IR, ^{1}Hnmr shown in table-2 .

3.2 Preparation of diamide of chrysanthemic acid.

The same procedure above was used to synthesize the diamide except two mole of λ-cyhalothrine were used to react with one mole of trimethoprim (2:1) was used. The diamide also obtained as a dark yellow after recrystallization from ethanol, other properties shown in table-2.

3.3 General procedure for the synthesis of amide-imines derivatives

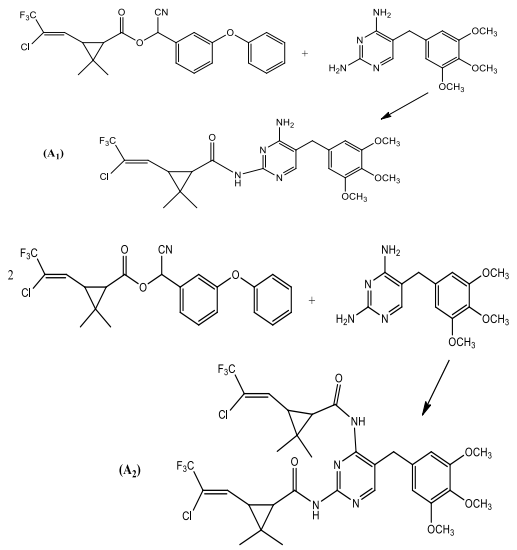
The same published procedure[15] with a little modification. Dissolve 0.5 m mole of the mono amide above in absolute ethanol and 0.5 m mole of aromatic aldehydes derivatives in a less amount of ethanol. To this mixture was added a few drops of phosphoric acid as a catalyst. The mixture was reflux in 150°C for 3 hrs. then cooled to room temp. The ppt. was filtered and washed with ethanol and recrystallize from ethanol. Physical properties shown in table for derivatives.

3.4 General method for synthesize of amide-azo derivatives

Dissolve 0.1 m mole from the monoamide 3.1 above in 3 ml of water acidified with 0.2 ml of concentrated hydrochloric acid. In another flask dissolve 0.7 m mole of $NaNO_2$ in 0.5 ml of water and the solution cooled to 5ºC. The diazonium salt prepared by the addition of the first solution drop wise to second solution while keeping the temperature less than 5ºC. To this diazonium salt added 0.1m mole of phenol or naphthol in 1 ml sodium hydroxide 10% with continuous stirring. The color of the solution clanged and the ppt. formed. The solution left stirring for additional 10 min. and neutralized with few drops of 5% HCl, then filtered off washed and dried.

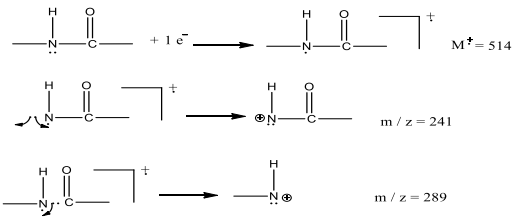
4- Results and Discussion

Mono amide was prepared by nucleophilic displacement of one amino groups of the trimethoprim with alcohol of λ-cyhalothrine in aquimolar amount. In the same way was prepared a di amide of trimethoprime and λ-cyhalothrine in 1:2 molar ratio as show in the following equations:

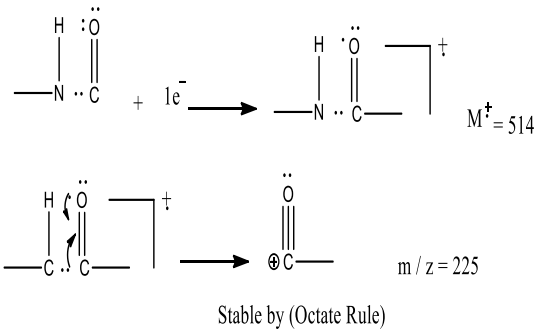


The compounds A_1 & A_2 were identified by their physical constant m.p. and FT-IR spectra which showed disappearance of the band at 1739cm^{-1} for the ester carbonyl and the appearance of new bond at 1634cm^{-1} for the amide carbonyl. The spectra also showed two strong stretching bands at (3470-3319) cm^{-1} belong to unreacted NH_2 and –NH for the amide. The band at 1565cm^{-1} was identified to C=N for the pyrimidine ring and the band at 1236cm^{-1} for C-N bond. The band at 3122cm^{-1} for aromatic C-H and the bands at (2930-2835) cm^{-1} for the C-H aliphatic. The ^{1}Hnmr spectra for A_1 indicated the appearance of the following bands at δ = 1.1 ppm for $–NH_2$ group and δ= 1.2 ppm for $–C(CH_3)_2$. δ = 1.7 ppm $–CH_2$- . δ = 2.2 ppm for cyclopropane ring –CH-CH-. Singlet at δ = 3.5 ppm for methoxy protons, δ = 5.2 ppm for amide proton –NH-CO, δ = 5.3 ppm identified for the alkene protons =CH. The band at δ = 7.2 ppm for aromatic protons. The A_2 showed the following bands δ = 1.2-1.3 ppm $[C(CH_3)_2]_2$, two bands at δ = 2.03-2.06 ppm for the-CH-CH- cyclopropane and a singlet band at δ= 2.18 for $–CH_2$ and δ = 4.01 for $–OCH_3$ protons, δ = 4.8 ppm for –NHCO, the signal at δ = 6.3 ppm belong to =CH alkene and δ = 6.3-7.7 ppm for aromatic protons. Other evidence come from mass spectrum for the compound A_1 showed the molecular ion $M^{\cdot+}$ = 514 which confirm the mono amide. This was also consistent with the nitrogen rule; and can give the molecular formula by application the thirteen number rule. Other fragmentation pattern can be explain as in the following:

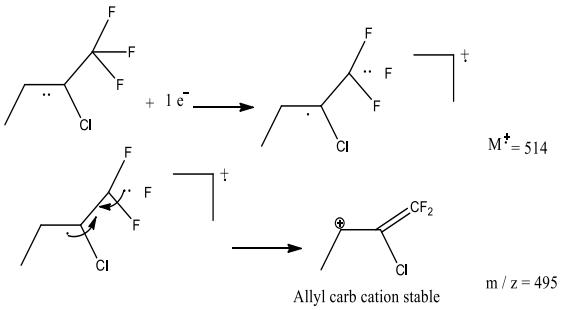
1- if the fragmentation take place from the pair of electron on the nitrogen atom, the mechanism as follow:



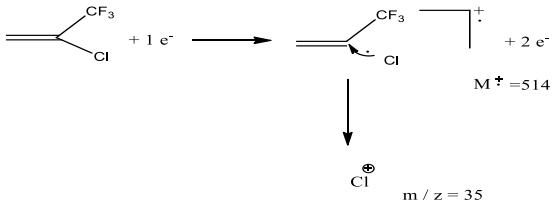
2- if it started from oxygen:



3- if it possibly occur from the alkene double bound:

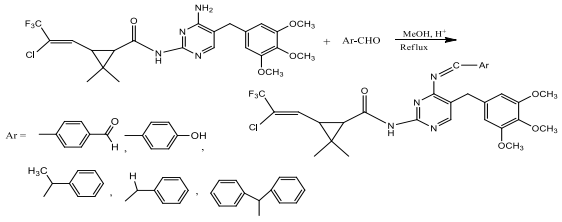


4- if it happen from the single σ-bond:



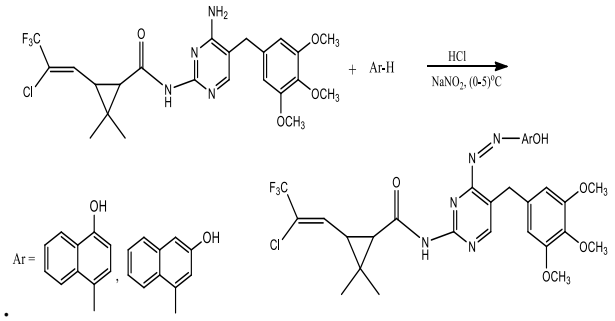
In all these mechanism the molecular ion appeared at $M^{+\cdot}$ = 514. The spectrum also showed the isotope fragment for the chlorine atom in a ratio (3:1),(35:37). Although compound A_2 did not give the molecular ion but the fragmentation pattern showed many fragment such as M,Z=514 and M/Z=225 which confirmed the formation of di amide (A_2).

Imines were prepared from the mono amide A_1 by treatment the later with some aromatic aldehydes and ketones to form amide-imine derivatives:



The products were confirmed by measurement of their melting points and recording the FT-IR of the target compound which show disappearance of stretching bonds at (1720-1740)cm^{-1} and (1705-1720)cm^{-1} for the carbonyl groups of aldehydes and ketones and appearance of absorption bonds at 1654-1678cm^{-1} for the azomethine C=N group of imines. Also the appearance of now bounds at (2785-2812) cm^{-1} for the imine proton(C-H) imine. Other bands for stretching and bending are shown in table. The mass spectra of some amide-imine derivatives as in (A_6) show the molecular ion M^{-}= 616 which consistence with the nitrogen rule and the rule of thirteen the presence of other fragments in the spectrum confirm the structure of the compound. Other derivatives, although did not give the molecular ion, the fragments at m/z = 104, m/z = 241 support the formation of amide and imine in the same compound. A_{10} gave fragments at m/z = 433, m/z = 450, m/z = 498 which are consistence with structure of amide-imines formation.

The azo compounds were prepared from A_1 by diazotization reaction using nitrous acid followed by treatment the intermediate diazonium salt with phenols or naphthols to give the corresponding azo derivatives



The compound were confirmed by their FT-IR and ^{1}Hnmr spectra of selected derivatives. The appearance of 1513cm^{-1} band which assigned to the azo group –N=N- and also abroad bands between 3420-3435 which assigned to the stretching frequencies for O-H groups of phenols and naphthols.^{1}Hnmr spectrum for A_4 showed the following signals: δ = 1.2 ppm assigned for –$C(CH_3)_2$;

δ = 2.2ppm for $–CH_2$; δ = 3.50 ppm belong to CH-CH- of cyclopropane. Δ = 3.52 ppm for $–O-CH_3$; δ = 5.3 ppm for NH-CO –amide, δ = 6.3 ppm for CH= alkene and the bands between 6.5-8.5 ppm belong to the aromatic proton.

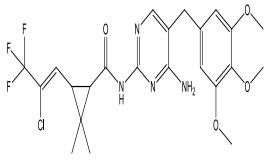
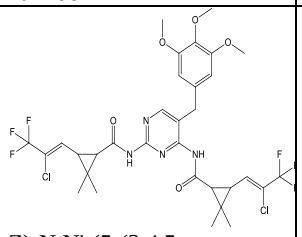
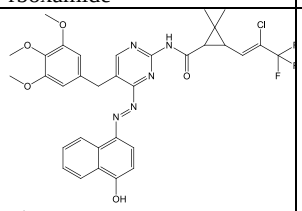
5- Biological Evaluation:

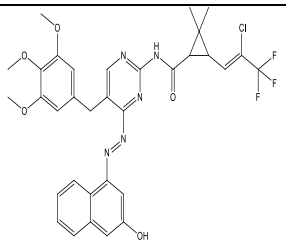
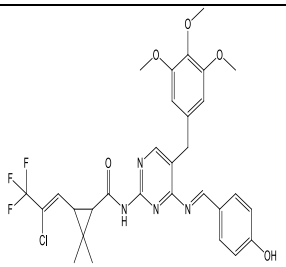
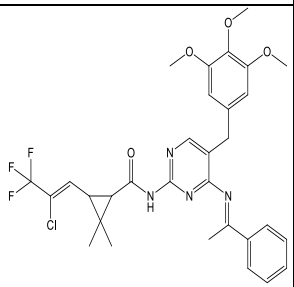
The final target of this research was to study the biological activity by investigating some of the compounds capacity to scavenge the free radical ($DPPH^{\cdot}$) at 50% concentration (IC50) using butylated hydroxyl toluene (BHT) as a control. This study reveals that the azo compounds (A_3, A_4) give highest scavenging activities, therefore it can be used as antioxidant suppliers. (table-1).

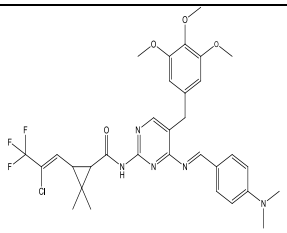
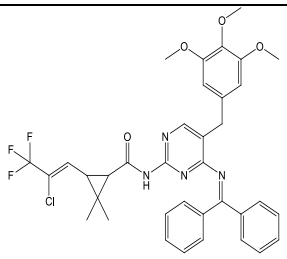
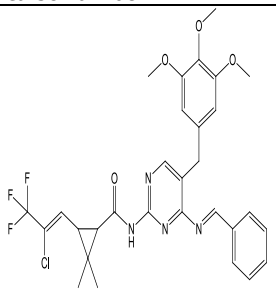
Table-1: Biological data for some prepared compounds as anti-oxidants

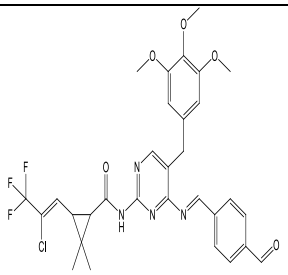
Sample	$DPPH^{\cdot}$ IC_{50} mg/ml
BHT	26.2
ƛ-cyhalothrin	320.53
A_1	150.2
A_2	111.6
A_3	80.7
A_4	90.2
A_5	222.6
A_6	190.5
A_7	112.3
A_8	108.1
A_9	177.6

Table-2: Molecular structure, physical properties and characteristics absorption frequencies for prepared compounds.

Comp.No.	Molecular structure and IUPAC Name	Color	M.P	Yield %	IR Characteristic Absorption Frequencies,cm^{-1}
A_1	 Z)-N-(4-amino-5-(3,4,5-) trimethoxybenzyl)pyrimidin -2-yl)-3-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethylcyclopropanecarboxamide	Pale yellow	180 -183	68	3470-3319 ν NH_2,N-H 3122 ν C-H arom. 2930-2835 ν CH_3 Alk. 1634 ν –NH-C=O Amid 1565 ν C=N 1263 ν C-N
A_2	 Z)-N,N'-(5-(3,4,5-)trimethoxybenzyl)pyrimidine-2,4-diyl)bis(3-((Z)-2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2dimethylcyclopropanecarboxamide	Dark yellow	182-185	61	3470-3319 ν N-H Amid 3122 ν C-H arom. 2930-2835 ν CH_3 Alk. 1634 ν –NH-C=O Amid 1565 ν C=N 1263 ν C-N
A3	 Z)-2-chloro-3,3,3-))-3trifluoroprop-1-en-1-yl)-N-(4-(Є-(4-hydroxynaphthalen-1-yl)diazenyl)-5-(3,4,5-trimethoxybenzyl)pyrimidin-2-yl)-2,2dimethylcyclopropanecarboxamide	Brown	-	77	3435 ν O-H Arom. 3047 ν C-H Arom. 2924 ν CH3 Alk. 1629 ν C=O Amid 1594 ν C=C Arom. 1513 ν N =N Azo.

A4	 Z)-2-chloro-3,3,3-))-3trifluoroprop-1-en-1-yl)-N-(4-((3-hydroxynaphthalen-1-yl)diazenyl)-5-(3,4,5-trimethoxybenzyl)pyrimidin-2-yl)-2,2-dimethylcyclopropanecarboxamide	Pale brown	-	57	3420 ν O-H Arom. 3047 ν C-H Arom. 2924 ν CH_3 Alk. 1629 ν C=O Amid 1601 ν C=C Arom. 1513 ν N =N Azo
A5	 Z)-2-chloro-3,3,3-))-3trifluoroprop-1-en-1-yl)-N-(4-((4-hydroxybenzylidene)amino)-5-(3,4,5-trimethoxybenzyl)pyrimidin-2-yl)-2,2-dimethylcyclopropanecarboxamide	white	202-205	80	3748-3409 ν O-H Arom. 3007 ν C-H Arom. 2897-2838 ν CH_3 Alk. 2812-2785 ν C-H Imin. 1678 ν C=N Imin. 1638 ν C=O Amid
A6	 Z)-2-chloro-3,3,3-))-3trifluoroprop-1-en-1-yl)-2,2-dimethyl-N-(4-((1-phenylethylidene)amino)-5-(3,4,5-trimethoxybenzyl) pyrimidin-2-yl) cyclopropanecarboxamide	Pale yellow	204-207	67	3179 ν C-H Arom. 2940-2338 ν CH_3 Alk. 1668 ν C=N Imin. 1639 ν C=O Amid 1591 ν C=C Arom. 1335,1321 ν C-O ethers

A7	 Z)-2-chloro-3,3,3-))-3trifluoroprop-1-en-1-yl)-N-(4-((4-(dimethylamino)benzylidene)amino)-5-(3,4,5-trimethoxybenzyl)pyrimidin-2-yl)-2,2-dimethylcyclopropanecarboxamide	Pale brown	205-208	66	3181 ν C-H Arom. 2917 ν CH_3 Alk. 1669 ν C=N Imin. 1639 ν C=O Amid 1595 ν C=C Arom. 1335 ν C=O ethers
A8	 Z)-3-(2-chloro-3,3,3-)trifluoroprop-1-en-1-yl)-N-(4-((diphenylmethylene)amino)-5-(3,4,5-trimethoxybenzyl)pyrimidin-2-yl)-2,2-dimethylcyclopropane carbox amide	Pale green	205-209	60	3185 ν C-H Arom. 2925 ν CH_3 Alk. 1678 ν C=N Imin. 1639 ν C=O Amid 1590 ν C=C Arom. 1340, 1321 ν C=O ethers
A9	 N-(4-(benzylideneamino)-5-(3,4,5-trimethoxybenzyl)pyrimidin-2-yl)-3-((Z)-2-chloro-3,3,3-trifluoroprop-1-en-1-yl)-2,2-dimethylcyclopropanecarboxamide	white		82	3062-3007 ν C-H Arom. 2896-2838 ν CH_3 Alk. 2811-2785 ν C-H Imin. 1681 ν C=N Imin. 1642 ν C=O Amid 1595 ν C=C Arom. 1242,1321 ν C-O ethers

A_{10}	 Z)-2-chloro-3,3,3-))-3trifluoroprop-1-en-1-yl)-N-(4-((4-formylbenzylidene)amino)-5-(3,4,5-trimethoxybenzyl)pyrimidin-2-yl)-2,2-dimethylcyclopropanecarboxamide	white	197-200	81	3121 ν C-H Arom. 2930 ν CH_3 Alk. 2834 ν C-H Alde. 1654 ν C=N Imin. 1634 ν C=O Amid. 1595 ν C=C Arom. 1235 ν C-O ethers

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تحضير وتشخيص مزيج من مركبات امايد- ايماين وامايد- ازو مشتقه من حامض الكريزينثامك والتراي ميثوبريم ودراسه فعاليتها الحيوية

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الخلاصة

ان حامض الكريزينثامك, التراي ميثوبريم, الامايدات, الايمايينات, ومركبات الازو جميعها تمتلك فعالية بايولوجيه في اتجاهات مختلفة, طبية وصيدلانيه وفي مجال المبيدات ....الخ. على هذا الاساس فأن ربط هذه المجاميع الوظيفية في مركب واحد بالأمكان ان يزيد من الفعالية، لذلك فأن البحث الحالي صمم لتحضير مزيج من الامايدات- الايمايينات وكذلك الامايدات- الازو مشتقة من التراي ميثوبريم كوحدة رئيسية (as a core) مع حامض الكريزينثامك, وذلك بتفاعل مولات متساوية من المركبات الأخيرة لتكوين امايدات احادية, والتي عند معاملة مجموعة الامين المتبقية في التراي ميثوبريم مع الالديهايدات الأروماتيه تعطي الامايينات المقابلة. او تعطي مركبات الازو عند مفاعلتها مع حامض النتروز ومن ثم مع الفينولات او النفثولات. وقد شخصت هذه المشتقات بواسطة الخواص الفيزياوية والطرق الطيفية مثل FT-IR , ^{1}Hnmr وطيف الكتلة لبعض المركبات المنتقاة. اضافه الى ذلك فأن الفعالية البايولوجية للمركبات المحضرة كمضادات للأكسدة (antioxidant) قد درست عن طريق قياس كفائتها لأقتناص الجذور الحرة ($DPPH^{\cdot}$) لتعطي منع في تركيز 50% (IC_{50}) وبأستعمال Butylated Hydroxyl Toluene (BHT) كمقياس وبينت الدراسة فعالية اقتناص كبيرة لمركبات الازو في هذا المجال.