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Convenient synthesis and anti-proliferative activity of some benzochromenes and chromenotriazolopyrimidines under classical methods and phase transfer catalysis

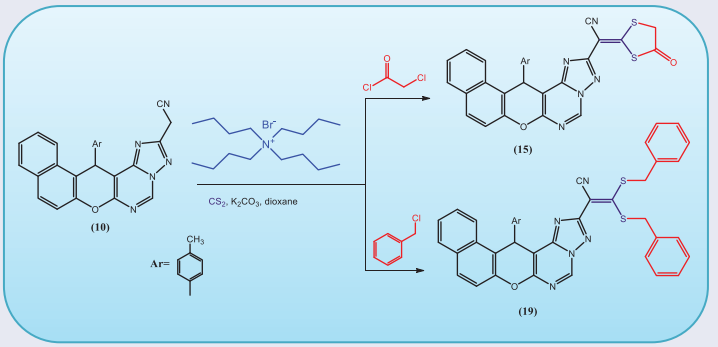
Amira T. Ali and Mohamed H. Hekal

Faculty of Science, Chemistry Department, Ain Shams University, Cairo, Egypt

ABSTRACT

A new series of benzochromene, benzochromenopyrimidine, and benzotriazolopyrimdine derivatives **3-10** were prepared via reaction of ethyl formimidate **2** with primary amines such as sulfanilamide, cyclohexylamine, 3-aminopyridine, 4-aminoantipyrine in addition to its reactions with different acid hydrazides. Compound **5** was further allowed to react with different *C*-electrophiles by classical and phase transfer catalysis conditions to get novel chromenotriazolopyrimidine derivatives. Screening of the antitumor activity in some of the newly synthesized compounds was tested *in vitro* against a panel of two human tumor cell lines namely HepG2 and HCT-116 cell lines. Compounds **4**, **7**, **8**, **10**, and **20** showed remarkable broad-spectrum antitumor activity.

GRAPHICAL ABSTRACT



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KEYWORDS
Benzochromenes; chromenotriazolopyrimidines; ethyl formimidate; phase transfer catalysis; antitumor activity

Introduction

Heterocycles containing the chromene moiety exhibit important features that make them an engaging target for synthesis. Chromenes represent a category of naturally occurring compounds.[1,2] The literature discloses that chromenes have a broad range of pharmacological activities such as antimicrobial,[3–7] antitumor.[8–11] For example,

CONTACT Mohamed H. Hekal mohahekal2007@yahoo.com Faculty of Science, Chemistry Department, Ain Shams University, Abbassia sq., Cairo 11566, Egypt.
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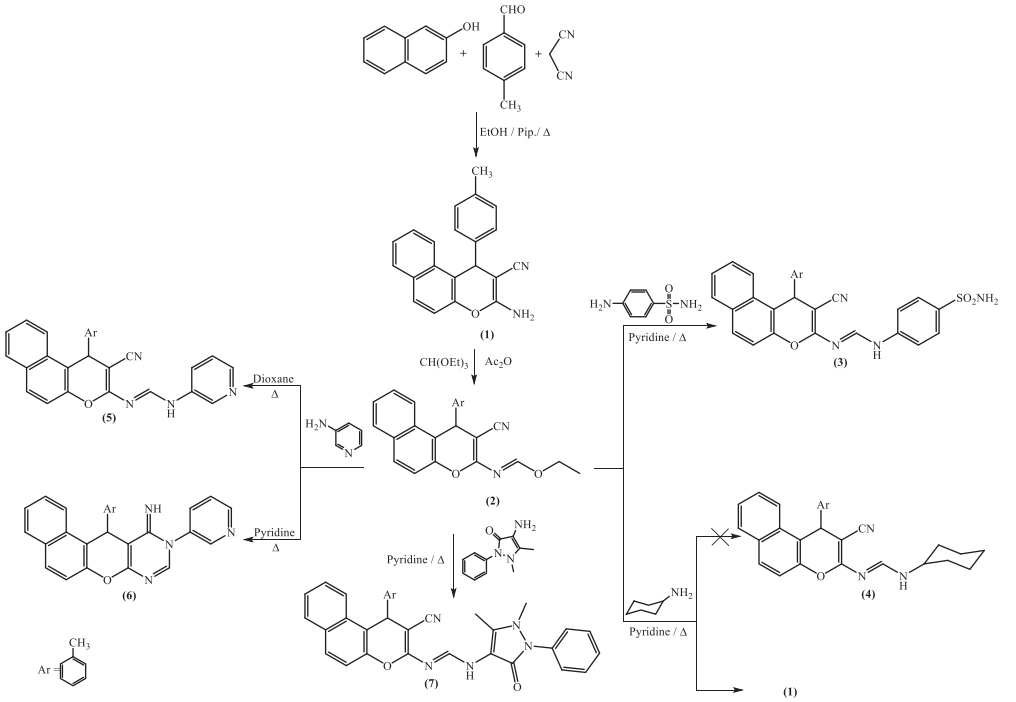


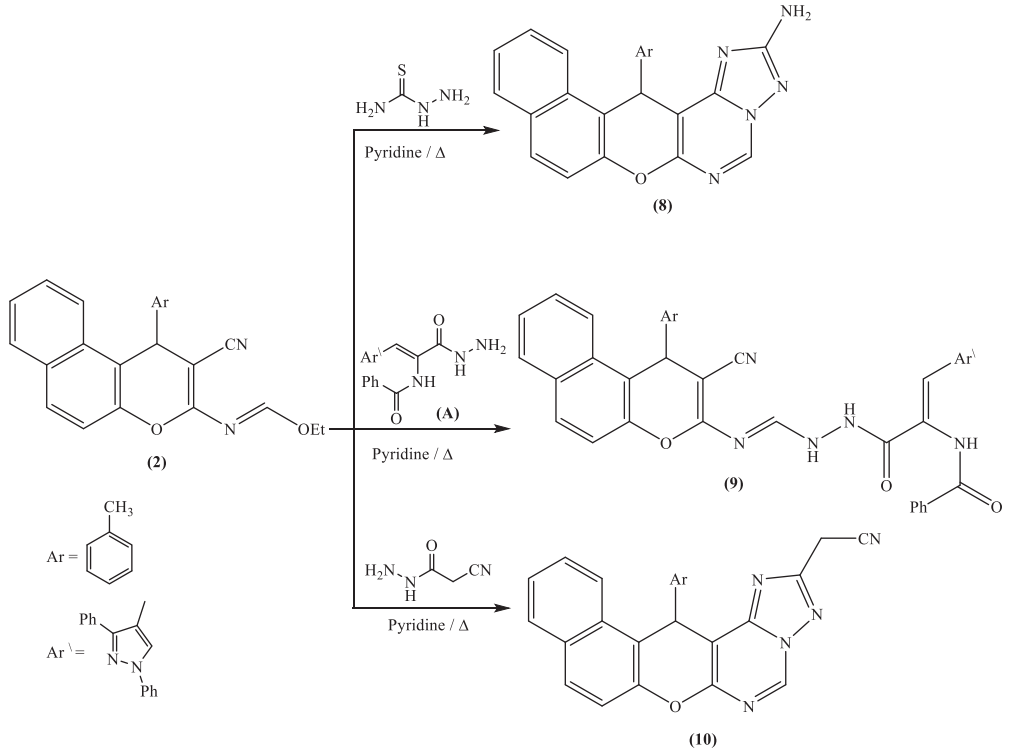
Scheme 1. Reaction of ethyl formimidate **2** with primary amines under conventional thermal conditions.

crolibulin is currently in phase II of clinical trials for the treatment of advanced solid tumors.[12] Also chromenes and benzochromenes exhibit other pharmacological activities such as antioxidant,[13,14] vasculardisurpting,[15] antileishmanial,[16] and analgesic.[17] On the other hand, triazolopyrimidines are a class of hybrid heterocycles of pyrimidine ring fused with triazole which having improved activity. 1,2,4-Triazolopyrimidine is one of important ring systems that has drawn the attention for its different biological activities as antiviral,[18] antimicrobial,[19,20] antitumor agents.[21–26] Phase transfer catalysis (PTC) has been used for the synthesis of organic compounds in both liquid-liquid and solid-liquid reaction mixtures to accelerate reaction rates by supporting formation of interphase transfer of molecules and making reactions between two phases possible. Applications of (PTC) in industrial processes supply great benefits for the environments.[27–32]

As a continuation our previous work on synthesis of heterocyclic compounds and using (PTC) in construction of new systems,[33–36] we report the synthesis of fused systems as benzo[f]chromenes, benzo[5,6]chromeno[2,3-d]pyrimidines, and benzo[5,6]-chromeno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines.

Result and discussion

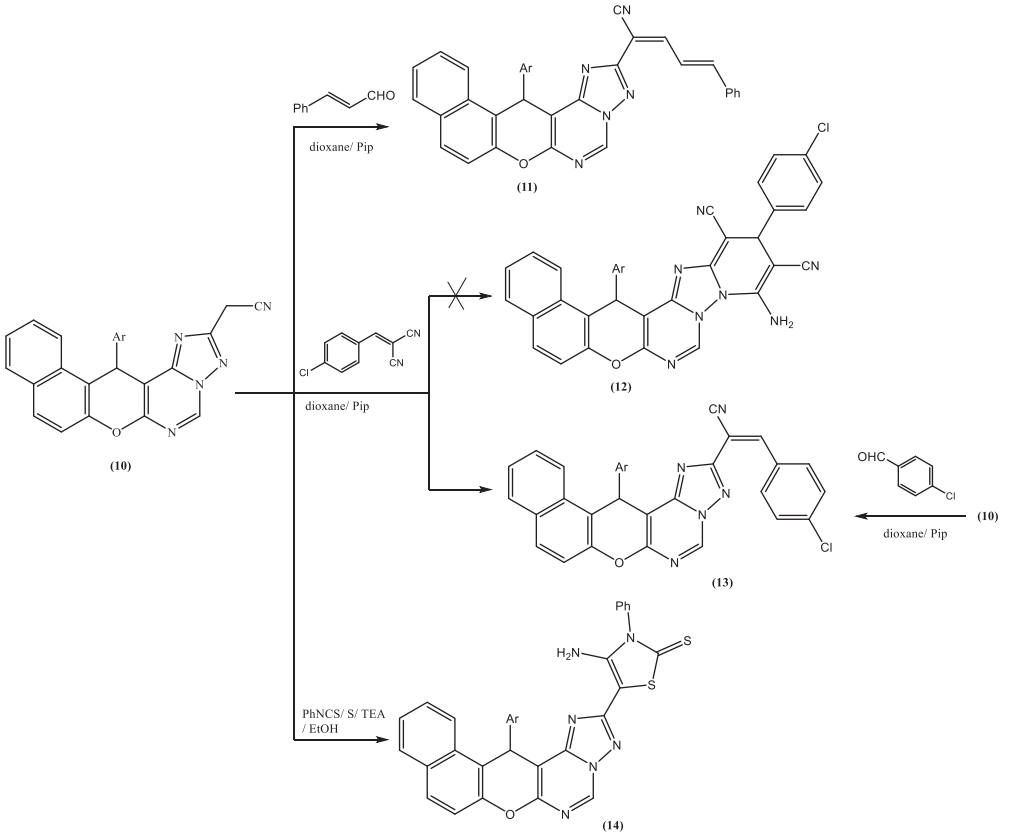
The starting material 3-amino-1-(p-tolyl)1-H-benzo[f]chromene-2-carbonitrile **1** was prepared according to the literature[37] through the treatment of malononitrile, p-methyl benzaldehyde and *β*-naphthol in the presence of catalytic amount of piperidine.



Scheme 2. Reaction of ethyl formimidate **2** with different acid hydrazides.

Refluxing of enaminonitrile **1** with triethyl orthoformate in the presence of freshly distilled acetic anhydride gave ethyl formimidate **2** which we then exploited for the syntheses of novel chromenopyrimidines and chromenotriazolopyrimidines was displayed to heating under reflux with different primary amines in either dioxane and/or dry pyridine (Scheme 1). Thus, Reaction of compound **2** with sulfanilamide in dry pyridine afforded the uncyclized formamidine derivative **3**. The supportive clue for the structure **3** deduced from the IR spectrum which showed absorption bands at 3194 (br.), 2185, and 1652 cm^{-1} corresponding to (NH, NH_2), (C≡N) and (C=N), respectively. During treatment of compound **2** with cyclohexylamine in either dioxane and/or dry pyridine a nonisolable addition product was formed first, followed by elimination of nonisolable ethyl-N-cyclohexylformimidate to return to the enaminonitrile **1** as a sole product. The spectroscopic data are in good agreement with the proposed structure (cf. experimental).

Aminolysis of compound **2** using 3-aminopyridine in boiling dioxane, formimidamide derivative **5** was formed. The structure of **5** was elucidated by elemental analysis and spectroscopic data. ^{1}H NMR of compound **5** revealed its existence as (*Z*, *E*)-isomers in the ratio 55:45 through the appearance of two singlet signals at δ 5.48, 5.51 ppm for pyran protons and two signals at 10.58, 11.03 ppm attributed for (NH) protons. Whereas the benzochromeno[2,3-d]pyrmidine derivative **6** was obtained by reaction of **2** with 3-aminopyridine in dry pyridine (Scheme 1). Adequate evidence for the cyclized structure **6** was substantiated from the correct elemental analysis and the spectral data. Thus, IR spectrum of **6** showed the appearance of absorption band for the NH group at

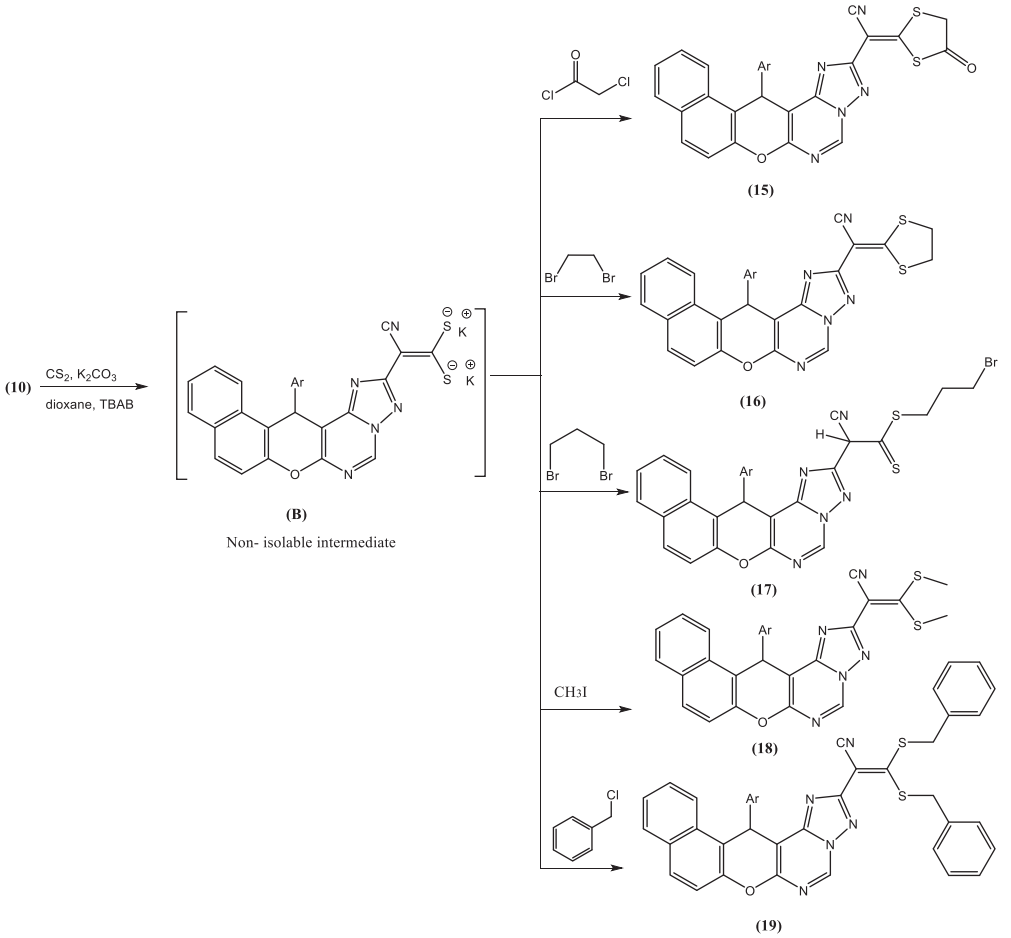


Scheme 3. Synthesis of triazolopyrimidine derivatives **11**, **13**, and **14**.

3274 cm^{-1} and along with the absence of any absorption band for the nitrile function is in agreement with the structure **6** as well as ^{1}H NMR spectrum is in favor with the suggested structure (cf. experimental).

Also refluxing compound **2** with 4-aminoantipyrine in either dioxane or dry pyridine gave formimidamide derivative **7**. The structure of new prepared compound **7** was established from its analytical and spectral data (cf. experimental).

Meanwhile, the reactivity of compound **2** with acid hydrazides namely, thiosemicarbazide, hydrazide derivative (**A**) and/or cyanoacetohydrazide has been reported (Scheme 2). Thus, triazolo[1,5-c]pyrimidine derivative **8** was obtained in fairly good yield upon refluxing the formimidate derivative **2** with thiosemicarbazide in dry pyridine. The structure of compound **8** was deduced by studying its spectroscopic data. Thus, the IR spectrum showed absence of the absorption band of the C≡N group in addition to the presence of NH_2 group at 3336 and 3169 cm^{-1}. While refluxing compound **2** with hydrazide derivative (**A**) in dry pyridine afforded the uncyclized derivative **9**. The structure of compound **9** was established from its analytical and spectral data (cf. experimental). On the other hand, treatment of ethyl formimidate **2** with cyanoacetohydrazide in dry pyridine gave chromenotriazolopyrimdine derivative **10** as the sole product in fairly good yield (Scheme 2). In the ^{1}H-NMR spectrum of compound **10**, the

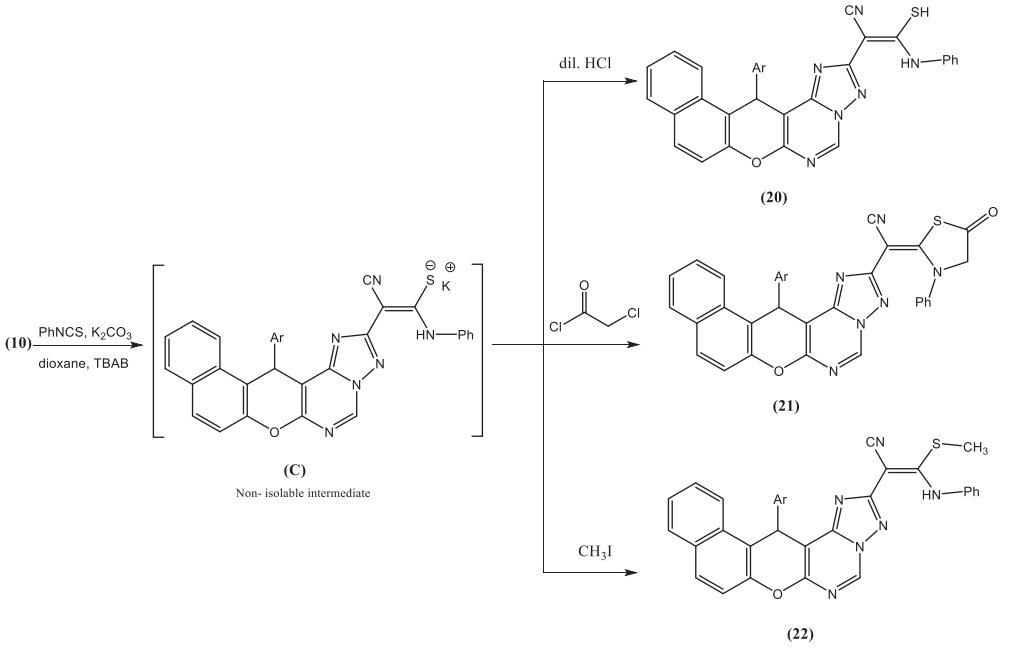


Scheme 4. Synthesis of chromenotriazolopyrimidine derivatives **15–19**.

appearance of a singlet signal attributable to the $-CH_2CN$ protons at δ 4.51 ppm confirmed the outcome of the cyclization reaction.

A number of chromenotriazolo[1,5-c]pyrimdines were synthesized using acetonitrile derivative **10** upon treatment with different *C*-electrophiles. Thus, condensation of compound **10** with cinnamaldehyde in refluxing dioxane and in the presence of catalytic amount of piperidine gave the corresponding arylidine derivative **11** (Scheme 3). The chemical structure of **11** was supported on the basis of elemental analysis and spectral data. Its IR spectrum showed absorption band at 2220 cm^{-1} for conjugated C≡N group.

Furthermore, the reactivity of triazolopyrimidine derivative **10** towards activated nitrile has been investigated as shown in Scheme 3. Thus, the reaction of compound **10** with 2-(4-chlorobenzylidine)malononitrile in refluxing dioxane in the presence of a catalytic amount of piperidine furnished the condensed product **13** instead enaminonitrile derivative **12**. This structure was confirmed by elemental analysis and spectral data. In addition, the strong evidence for the structure **13** is forthcoming from an authentic sample prepared from condensation of compound **10** with *p*-chlorobenzaldehyde in



Scheme 5. Synthesis of chromenotriazolopyrimidine derivatives **20–22**.

refluxing dioxane in the presence of catalytic amount of piperidine (TLC, mp and IR comparison) (Scheme 3). Also, the absence of a broad singlet in the ^{1}H-NMR spectrum corresponding to NH_2 argued against the formation of the putative enaminonitrile derivative **12**.

Moreover, The Gewald reaction[38] of compound **10** with elemental sulfur and phenyl isothiocyanate in absolute ethanol containing triethylamine as a basic catalyst led to functionalized thiazoline **14**. (Scheme 3). The structure of the prepared compound was elucidated on the basis of elemental analysis and spectral data. The IR spectrum of thiazoline **14** revealed the absence of C≡N absorption band and the presence of new absorption bands at 3442, 3318 cm^{-1} assignable to the amino group and a band at 1228 cm^{-1} due to C=S group. Furthermore, ^{1}H NMR spectrum was characterized by the existence of thiazolopyrimidine H-5 at δ 9.79 ppm as well as a singlet signal at δ 6.98 ppm for NH_2 protons exchangeable by D_2O.

In this study, acetonitrile derivative **10** was utilized as a precursor for synthesis of biologically active triazolopyrimdine derivatives under phase transfer catalysis conditions using solid-liquid phase system (dioxane/K_2CO_3/tetrabutyl ammonium bromide (TBAB)), where the reactants in dioxane existed in organic phase in which K_2CO_3 was suspended. The reaction mechanism includes two consecutive catalytic cycles, the first one proton abstraction from nucleophile occurs on solid carbonate surface then the formed anion immigrates as ion-pair into the organic phase in which the second step concerned with substitution occurred.[39] The one-pot reaction of compound **10** with dihalo-compounds namely chloroacetyl chloride, 1,2-dibromoethane, 1,3-dibromopropane and/or monohalo-compounds such as methyl iodide, benzyl chloride in dioxane in the presence of carbondisulphide as a reactant under PTC conditions (Scheme 4) afforded triazolopyrimdine derivatives **15–19**. The structures of these compounds were

Table 1. Cytotoxicity (IC_{50}) of the tested compounds on different cell lines.

	In vitro cytotoxicity IC_{50} (μM)[a]	
Compounds no.	HePG2	HCT-116
1	14.81 ± 1.3	9.37 ± 0.8
3	36.49 ± 2.7	11.21 ± 1.1
5	31.50 ± 2.4	38.67 ± 2.5
6	49.23 ± 2.9	53.03 ± 3.2
7	6.18 ± 0.5	4.98 ± 0.4
8	8.49 ± 0.7	7.61 ± 0.6
9	43.56 ± 2.6	48.28 ± 2.9
10	10.05 ± 1.0	8.12 ± 0.7
11	17.32 ± 1.6	19.74 ± 1.5
13	93.32 ± 5.2	86.14 ± 4.9
14	58.17 ± 3.5	16.35 ± 1.4
16	24.84 ± 2.1	30.42 ± 2.3
17	72.98 ± 4.6	79.60 ± 4.3
18	67.90 ± 3.6	74.16 ± 3.8
19	54.06 ± 3.2	61.59 ± 3.6
20	4.26 ± 0.3	3.19 ± 0.2
22	18.62 ± 1.9	23.61 ± 1.8
DOX	4.50 ± 0.2	5.23 ± 0.3

[a]IC_{50} (μM): 1–10 (very strong), 11–20 (strong), 21–50 (moderate), 51–100 (weak), above 100 (non-cytotoxic). **DOX**: Doxorubicin.

evidenced by studying their elemental analyses and spectroscopic data. Thus, the appearance of conjugated nitrile at lower frequency in the IR spectra of compounds **15**, **16**, **18**, and **19** than that observed with the title compound **10** were in agreement with the suggested structures.

The formation of 1,3-dithiolanone derivative **15** has been deduced from appearance of the absorption band at 1731 cm^{-1} for C=O group in IR spectrum as well as the presence of a singlet signal in ^{1}H-NMR spectrum at 4.51 ppm for (S–CH_2–CO). The appearance of two triplet signals at δ 3.79 and 3.87 ppm for (–CH_2–CH_2–) of compound **16** is completely in agreement with the proposed structure whereas ^{1}H-NMR spectrum of **17** showed triplet signal at 2.28 for central (–CH_2–), triplet at 3.21 for (S–CH_2–), triplet at 3.24 for (–CH_2–Br) and singlet signal at 4.51 ppm for (–CHCN–) which confirmed the uncyclized structure. In addition, the structures of triazolo[1,5-c]pyrimdines **18** and **19** were established from their analytical and spectral data (cf. experimental).

To show the synthetic potentiality of compound **10**, the reactivity of **10** with isothiocyanates was investigated. Thus, one pot reaction of benzochromeno[1,2,4]triazolo[1,5-c]pyrimdine derivative **10** with phenyl isothiocyanate in dioxane and tetrabutylammonium bromide (TBAB) under PTC conditions afforded the non-isolable intermediate (**C**), which was converted *in situ* to the newly synthesized compounds **20–22** (Scheme 5) upon treatment with hydrochloric acid, chloroacetylchloride and methyl iodide, respectively. The structures of the latter products were established on the basis of elemental analysis, spectral data. The appearance of a cyano absorption band around 2175 cm^{-1} in their IR spectra in addition of a band at 1728 cm^{-1} for C=O in case of thiazolidinone derivative **21**. ^{1}H-NMR spectra of these compounds are in agreement with the assigned structures (cf. experimental).

We evaluated the cytotoxicity of the synthesized compounds against two human tumor cell lines (Table 1, Figure 1). The cell lines were hepatocellular carcinoma (HePG-2) and colon cancer (HCT-116). In general, the cytotoxic activity of the

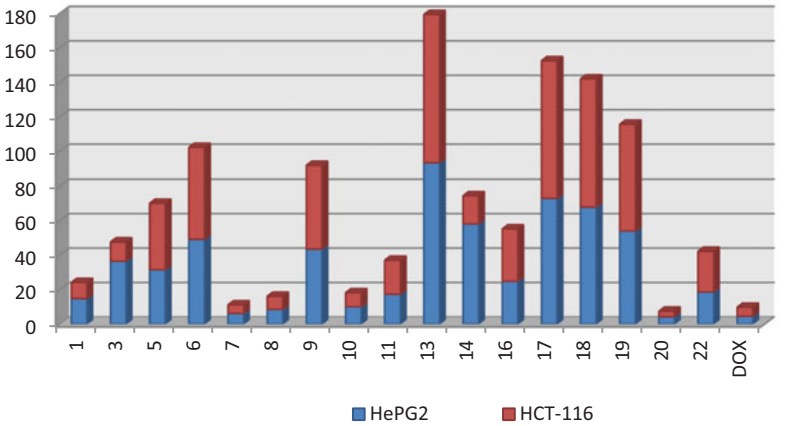


Figure 1. Cytotoxic activity of the tested compounds on different cell lines.

examined compounds ranged from very strong to weak activity. The optimal results were observed for compounds **7**, **8**, and **20** which showed IC_{50} 6.18 ± 0.5, 8.49 ± 0.7, and 4.26 ± 0.3 μM for the HePG-2 cell line, respectively. While compounds **1**, **7**, **8**, **10**, and **20** showed very strong activities with IC_{50} 9.37 ± 0.8, 4.98 ± 0.4, 7.61 ± 0.6, 8.12 ± 0.7, and 3.19 ± 0.2 μM for the HCT-116 cell line, respectively.

Structure-activity relationship (SAR)

By comparing the experimental cytotoxicity of the compounds reported in this study to their structures, the following SAR was postulated.

- Compound **7** showed very strong cytotoxic activity, this is maybe due to the presence of antipyrine ring.
- Compound **8** showed very strong cytotoxic activity, this is due to the presence of NH_2 group which is available to form a hydrogen bond with either one of the nucleobases of the DNA and causes its damage.
- Compound **20** showed very strong activity, this is due to the presence of NH and SH groups which may add to any unsaturated moiety in DNA or forming a hydrogen bond with either one of the nucleobases of the DNA and causes it damage.

Materials and methods

Chemistry

All melting points were taken on a Griffin and George melting-point apparatus (Griffin & George Ltd., Wembley, and Middlesex, UK) and are uncorrected. IR spectra were recorded on Pye Unicam SP1200 spectrophotometer (Pye Unicam Ltd., Cambridge, UK) by using the KBr wafer technique. ^{1}H-NMR spectra were determined on a Varian Gemini 400 MHz by using tetramethylsilane as internal standard (chemical shifts in δ scale). Elemental analyses were carried out at the Microanalytical Unit, Faculty of

Science, Ain Shams University, using a Perkin-Elmer 2400 CHN elemental analyzer (Waltham, MA), and satisfactory analytical data (±0.4) were obtained for all compounds. The homogeneity of the synthesized compounds was controlled by thin-layer chromatography (TLC), using aluminum sheet silica gel F_{254} (Merck). The antitumor activities were performed at Microanalytical Center of Mansoura University, Egypt.

3-amino-1-(p-tolyl)-1H-benzo[f]chromene-2-carbonitrile 1

A solution of malononitrile (0.66 g, 10 mmol), *p*-methylbenzaldehyde (1.2 ml, 10 mmol), and *β*-naphthol (1.44 g, 10 mmol) in absolute ethanol (30 ml) containing piperidine (0.5 ml) was heated under reflux for 2 h. The deposited solid was filtered off, dried and then crystallized from ethanol to give **1** as white crystals, 90% yield, mp 272–273 °C [Lit. mp: 268–269 °C].

Ethyl (E)-N-(2-cyano-1-(p-tolyl)-1H-benzo[f]chromen-3-yl)formimidate 2

A solution of enaminonitrile **1** (3.12 g, 10 mmol) and triethylorthoformate (6 mL, 30 mmol) and acetic anhydride (15 mL) was heated at reflux for 6 h. The formed solid was filtered off, dried, and then crystallized from ethanol to give **2** as pale yellow crystals, 88% yield, mp 160–162 °C. IR (KBr, ν, cm^{-1}): 3019 (CH aromatic), 2208 (C≡N), 1653 (C=N). Anal. Calcd. for $C_{24}H_{20}N_2O_2$ (368.44): C, 78.24; H, 5.47; N, 7.60. Found: C, 78.32; H, 5.53; N, 7.57.

Cytotoxicity assay

The cytotoxic activity of eleven compounds was tested against two human tumor cell lines namely: hepatocellular carcinoma (liver) HePG-2 and colon cancer (HCT-116). The cell lines were obtained from the ATCC via the Holding Company for Biological Products and Vaccines (VACSERA, Cairo, Egypt). Doxorubicin was used as a standard anticancer drug for comparison. The reagents used were RPMI-1640 medium, MTT, DMSO and 5-fluorouracil (Sigma Co., St. Louis, MO, USA), and Fetal Bovine Serum (GIBCO, Paisley, UK).

The different cell lines[40,41] mentioned above were used to determine the inhibitory effects of compounds on cell growth using the MTT assay. This colorimetric assay is based on the conversion of the yellow tetrazolium bromide (MTT) to a purple formazan derivative by mitochondrial succinate dehydrogenase in viable cells. The cells were cultured in RPMI-1640 medium with 10% fetal bovine serum. Antibiotics added were 100 units/mL penicillin and 100 µg/mL streptomycin at 37 °C in a 5% CO_2 incubator. The cell lines were seeded[42] in a 96-well plate at a density of 1.0×10^4 cells/well at 37 °C for 48 h under 5% CO_2 incubator. After incubation the cells were treated with different concentration of compounds and incubated for 24 h. After 24 h of drug treatment, 20 µL of MTT solution at 5 mg/mL was added and incubated for 4 h. Dimethyl sulfoxide (DMSO) in volume of 100 µL was added into each well to dissolve the purple formazan formed. The colorimetric assay is measured and recorded at absorbance of 570 nm using a plate reader (EXL 800, BioTech, Winoosky, VT, USA).

The relative cell viability in percentage was calculated as (A_{570} of treated samples/ A_{570} of untreated sample) × 100.

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